Studies towards the total synthesis of cycloaraneosene

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Studies Towards the Total Synthesis of Cycloaraneosene

Submitted by Jean-Philippe Cros

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ABSTRACT

Investigative studies towards the total synthesis of cycloaraneosene, a natural product containing a [5-8-5] tricyclic carbon backbone, have been conducted, based on a novel convergent synthetic strategy.

The right hand, five-membered ring C was synthesised in two steps from commercially available 1,3-cyclopentadione. A model study, directed towards the synthesis of the core [8-5] bicyclic system B-C, was then investigated in order to assess the feasibility of the key steps in the overall synthetic approach. Thus, the formation of the [8-5] carbon framework *via* the ring-closing metathesis of the adequate triene precursor was methodically explored with first and second generation Grubbs' catalysts. Subsequently, a Cu mediated 1,4-addition was performed on the resulting bicyclic enone, thereby introducing the quaternary methyl group at the ring-junction. Palladium-mediated coupling of the isopropyl side-chain was also examined on a closely related monocyclic system.

On the other hand, a synthetic strategy was designed and applied to the synthesis of five-membered ring A. Firstly, efforts were devoted towards the generation of the *gem*-alkene exocyclic side-chain. As a result, four *gem*-alkene derivatives were obtained in a maximum of three steps, from readily available starting materials. Then, from 2-cyclopentenone, systematic studies based on the Noyori three-component coupling synthesis of prostaglandins afforded a rapid entry to three polysubstituted five-membered rings. Furthermore, two adjacent synthetic routes were investigated leading to two novel α,β-unsaturated esters. From these enoates, copper mediated 1,4-addition was examined. Finally, an alternative and rapid entry

towards ring A was designed *via* an unprecedented 1,4-addition/elimination reaction with a β-carbonate enoate.

The stereochemical aspects were also considered, when appropriate, in each individual chapter.

A la mémoire de mon grand-père: "Fais des études ...."

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CONTENTS

Abbreviations

Ac	Acetate
AIBN	Azoisobutyronitrile
app.	Apparent
Ar	Aryl
ATP	Adenosine triphosphate
9-BBN	9-Boracyclo[3.3.1]nonane
Bn	Benzyl
bp	Boiling point
bs	Broad singlet
BSA	*N,O*-Bis(trimethylsilyl)acetamide
Bu	Butyl
CI	Chemical ionisation
Conc.	Concentration
Cq	Quaternary carbon
Cy	Cyclohexyl
d	Doublet
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]-7-undec-7-ene
DCM	Dichloromethane
de	Diastereomeric excess
DIBAL	Diisobutylalumium hydride
DHP	Dihydropyrane
DMAP	4-Dimethylaminopyridine

DME	1,2 Dimethoxyethane
DMF	*N,N'*-Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
dppe	1,2-*Bis*(diphenylphosphino)ethane
dppf	*Bis*(diphenylphosphino)ferrocene
E	Electrophile
eq.	Equivalent
EI	Electron impact
ES	Electrospray
Et	Ethyl
FAB	Fast atom bombardment
g	Gram
GC	Gas Chromatography
HMPA	Hexamethylphosphoramide
imid	Imidazole
i-Pr	Isopropyl
IR	Infra red
KHMDS	Potassium hexamethyldisilylazide
LDA	Lithium diisopropylamide
liq	Liquid
M	Metal
m	Multiplet
m-CPBA	*Meta*-chloroperbenzoic acid
Me	Methyl

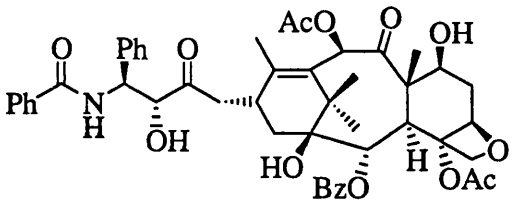
mg	Milligram
mL	Millilitre
mm	Millimetre
Mp	Melting point
NMR	Nuclear magnetic resonance
P	Protecting group
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Pd-C	Palladium on charcoal
Ph	Phenyl
PMA	Phosphomolybdic acid
PPTS	Pyridinium *para*-toluene sulfonate
p-TSA	*Para*-toluenesulfonic acid
Pyr.	Pyridine
RCM	Ring closing metathesis
Red-Al	Sodium *bis*(2-methoxyethoxy)aluminium hydride
s	Singlet
SN2	Nucleophilic substitution bimolecular
TBAF	Tetrabutylammonium fluoride
TBDMS	*Tert*-Butyldimethylsilyl
TBS	Tetrabutylsilyl
Tf	Trifluoromethyl sulfonate
TFP	2,2,3,3-Tetrafluoropropan-1-ol
THF	Tetrahydrofuran
THP	Tetrahydopyran
TIPS	Tri*iso*propylsilyl

TLC	Thin layer chromatography
TMS	Tetramethylsilane
TMSCl	Trimethylsilylchloride
Ts	*Para*-toluenesulfonyl
UV	Ultra violet
X	Halogen

Chapter 1:

Introduction and Synthetic Strategy

There are over one hundred known terpenoid natural products containing an eight-membered ring carbocycle in their structures; they have been classified in several families according to their carbon backbone [1]. The most prominent of all, the taxane family, is one of them and the efforts devoted towards the total synthesis of Taxol® [2] summarises the synthetic challenges associated with this type of natural products: a carbon framework containing an eight-membered ring and bearing a complex stereochemistry.



(-)-Taxol

Figure 1.1: The structure of Taxol®

The [5-8-5] tricyclic ring system of the fussicoccane family presents similar synthetic challenges.

1.1 Structure and biological activity

The fusicoccanes belong to the diterpenoid family (originating from four isoprene unit).

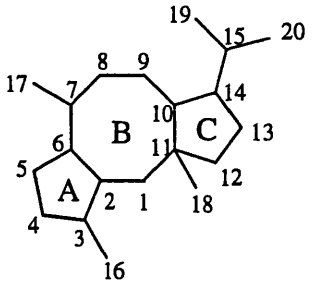


Figure 1.2: General structure of the fusiccocanes.

These natural products are fungal toxins, which markedly affect physiological process in higher plants [3] by stimulating growth and H^+ excretion [4]. At the cell physiological level, their action consists of the activation of the H^+ ATPase.

The structure of cycloaraneosene, a member of this class of natural products, is depicted below:

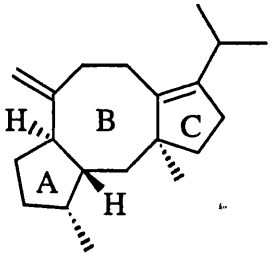
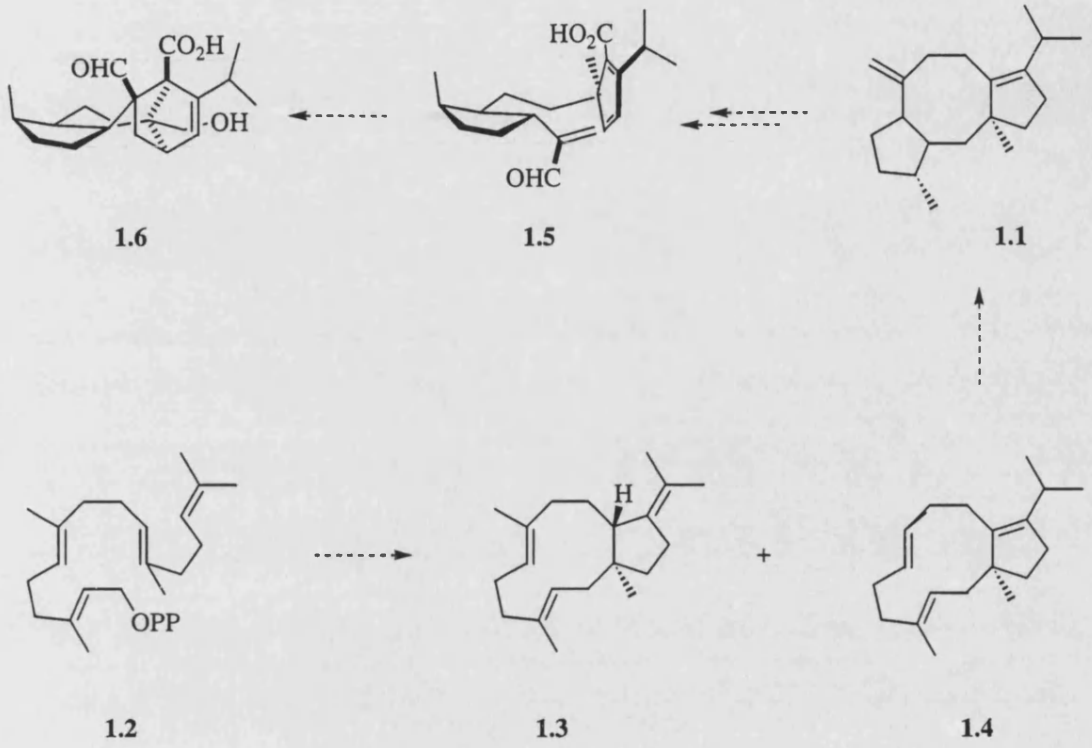


Figure 1.2: Structure of cycloaraneosene

Cycloaraneosene was first extracted in 1975 from the mould *sordaria araneosa* [5]. It is believed to be a metabolite of this plant and an intermediate in the proposed biogenetic pathway below [5]:



1.6 **1.5** **1.1**

1.2 **1.3** **1.4**

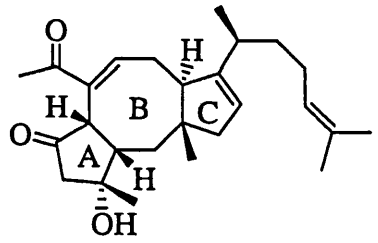
Scheme 1.1: Biogenetic pathway

Dolabellanes diterpenes **1.3** and **1.4** are derived from the acyclic precursor geranylgeraniol **1.2**. These bicyclic metabolites are believed to be biogenetically transformed into cycloaraneosene *via* an acid-induced cyclisation. In turn, cycloaraneosene is ring-opened and oxidised to the acid **1.5**, the biogenetic precursor of sordarin **1.6**.

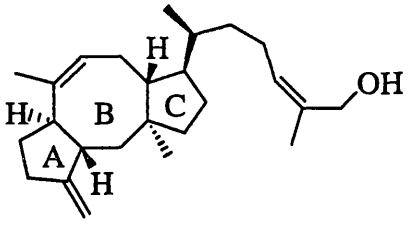
The first striking feature when examining the structure of cycloaraneosene is the absence of any heteroatom. A *tetra*-substituted alkene in ring C and an exocyclic double bond off ring B are the only functionalities present in this natural product.

Within its framework, cycloaraneosene contains four stereocentres: at C_3 in ring A, two at the ring junction A-B (*trans* geometry) and finally a quaternary carbon centre at the ring junction B-C in C_{11}. The isopropyl exocyclic chain, off ring C, is typical of the fusicoccane compounds.

Cycloaraneosene is also structurally related to other classes of natural products: the ophiobolanes and the ceroplastins (a sub-class of the ophiobolanes). These sesterterpenes (five isoprene units) contain the same [5-8-5] tricyclic carbon backbone but the exocyclic side-chain attached to ring C is longer. Typical examples, ophiobolin M and ceroplastol I are shown **Figure 1.3**:



ophiobolin M



ceroplastol I

Figure 1.3

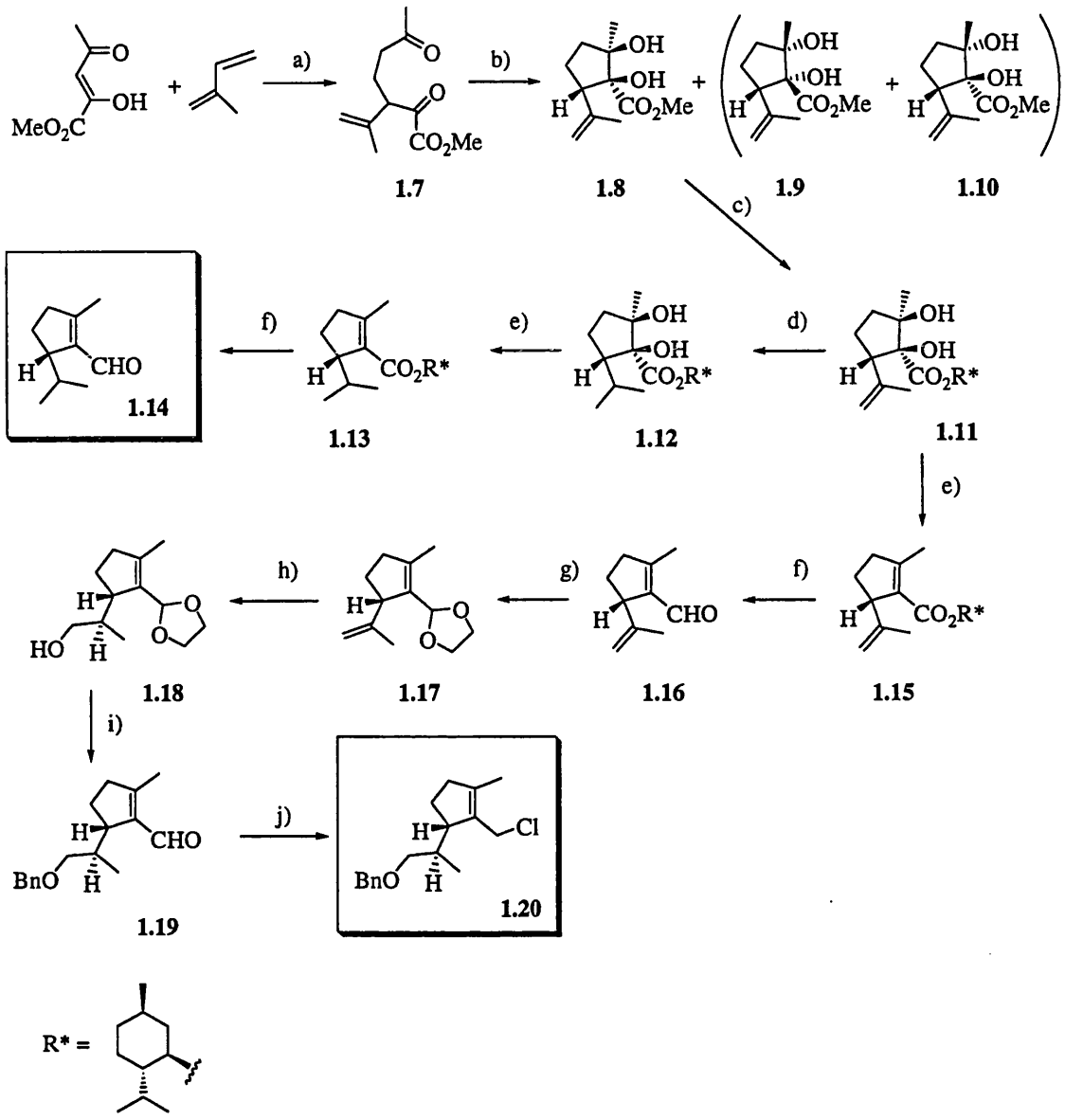
1.2 Selected literature precedence on the construction of [5-8-5] tricyclic systems

Considerable synthetic efforts have been devoted towards the synthesis of [5-8-5] tricyclic systems [6]. Different types of strategies have been designed to overcome the problematic construction of the central eight-membered ring and to tackle the often complex stereochemistry of these natural products. Several representative approaches are outlined below. They can be divided into five different synthetic strategies with respect to the construction of the tricyclic carbon backbone: the convergent assembly

of two five-membered rings, [4+4] cycloadditions of a suitable precursor, ring-expansion of more accessible medium-size rings, ring-fragmentation of polycyclic systems and ring contraction of a macrocyclic system.

1.21 *The convergent assembly of two five-membered rings.*

Takeshita and co-workers have already applied a successful convergent approach to the total synthesis of cycloaraneosene [7]. They first reported the synthesis of both enantiopure natural products iridoïds **1.14** and **1.20,** respectively the right and left hand-side of the molecule in their strategy [8]:



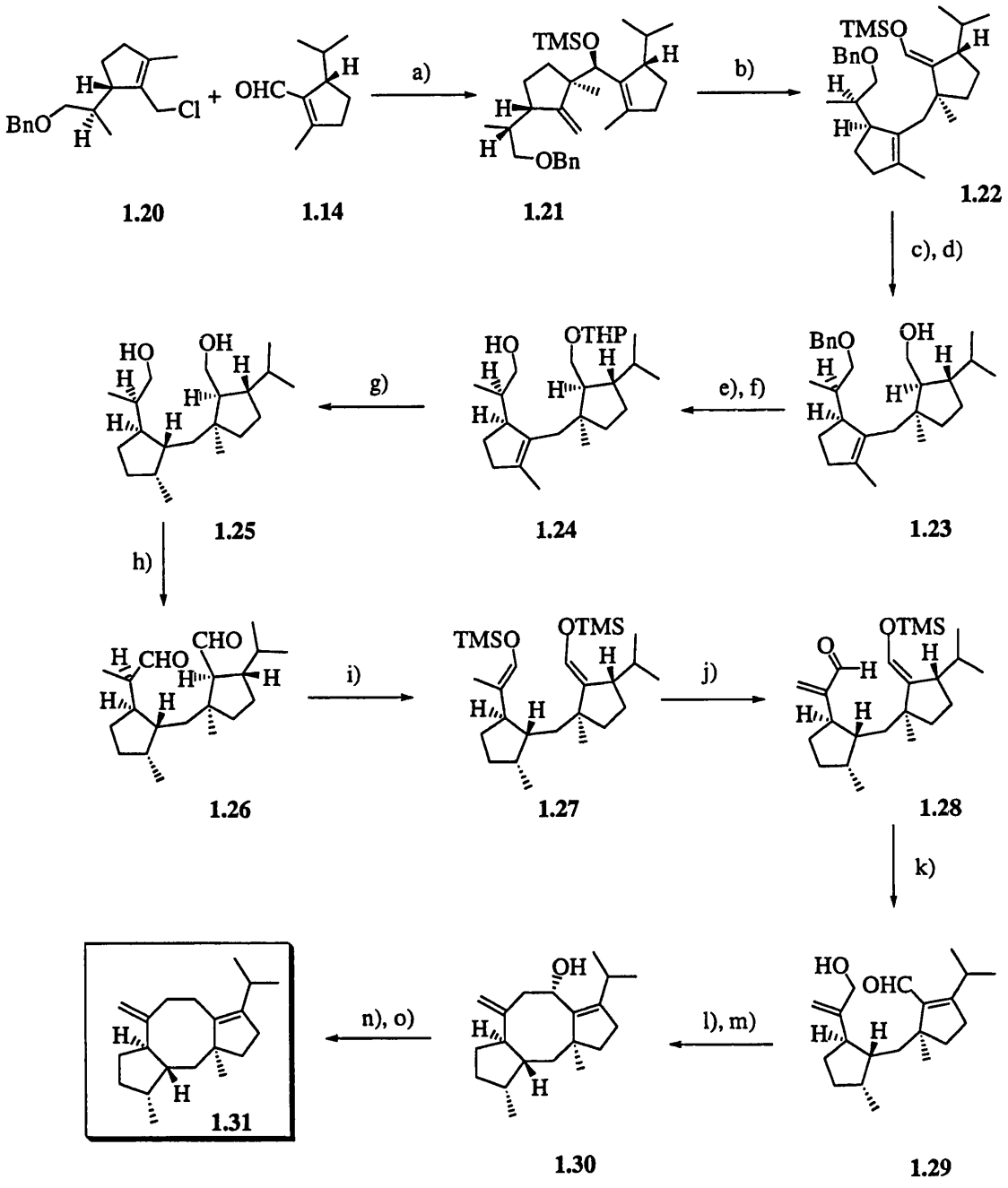
Scheme 1.2: Former total synthesis of cycloaraneosene, first part.

a) hv; b) $TiCl_4$-Zn, THF 68 %; c) i: $HC(OMe)_3$, ii: potassium *l*-menthoate, iii: AcOH, iv: $KHCO_3$, v: fractional crystallisation in hexane-EtOAc, 1:1, 49 % over 5 steps; d) H_2, Pd-C, MeOH 100 %; e) i: $HC(OMe)_3$, ii: Ac_2O, heat, 99 % for **1.13**, 98 % for **1.15**, both over 2 steps; f) i: DIBAL, toluene ii: MnO_2, CH_2Cl_2, 61 % for **1.14**, 83 % for **1.16** both over 2 steps; g) Ethylene glycol, PPTS, benzene, 91 %, h) i: $NaBH_4$, $BF_3.Et_2O$, DME, ii: NaOH, H_2O_2, 83 % over 2 steps, i) i: BnCl, NaH, DMF, ii: HCl, Et_2O, 72 %; j) i: $NaBH_4$, MeOH, ii: $(COCl)_2$, DMSO, CH_2Cl_2, 92 % over 2 steps.

Firstly, a [2+2] cycloaddition of 2,4-dioxopentanoate with isoprene provided intermediate **1.7** [9], which was cyclised *via* a titanium(II) chloride mediated

cyclisation to afford diols **1.8**, **1.9** and **1.10** [10]. Resolution by fractional recrystallisation, with an enantiomerically pure menthyl auxiliary derivative, effectively separated the diols. Then, the double bond was reduced to give diol **1.12**. From **1.12**, dehydration followed by reduction of the ester with diisobutylaluminium hydride and subsequent oxidation of the resulting allylic alcohol provided unsaturated aldehyde **1.14**. Following the same sequence, diol **1.11** was transformed into the aldehyde **1.16**, which was protected with ethylene glycol. Selective hydroboration of the least substituted double bond led to **1.18**. Benzylation followed by deprotection gave aldehyde **1.19**. Finally, reduction with $NaBH_4$ followed by chlorination with $(COCl)_2$ in DMSO provided iridoïds **1.20**.

Building blocks **1.14** and **1.20** were then coupled *via* a $CrCl_2$ mediated condensation followed by subsequent protection of the secondary alcohol functionality [11] to yield the dicyclopentane derivative **1.21**:

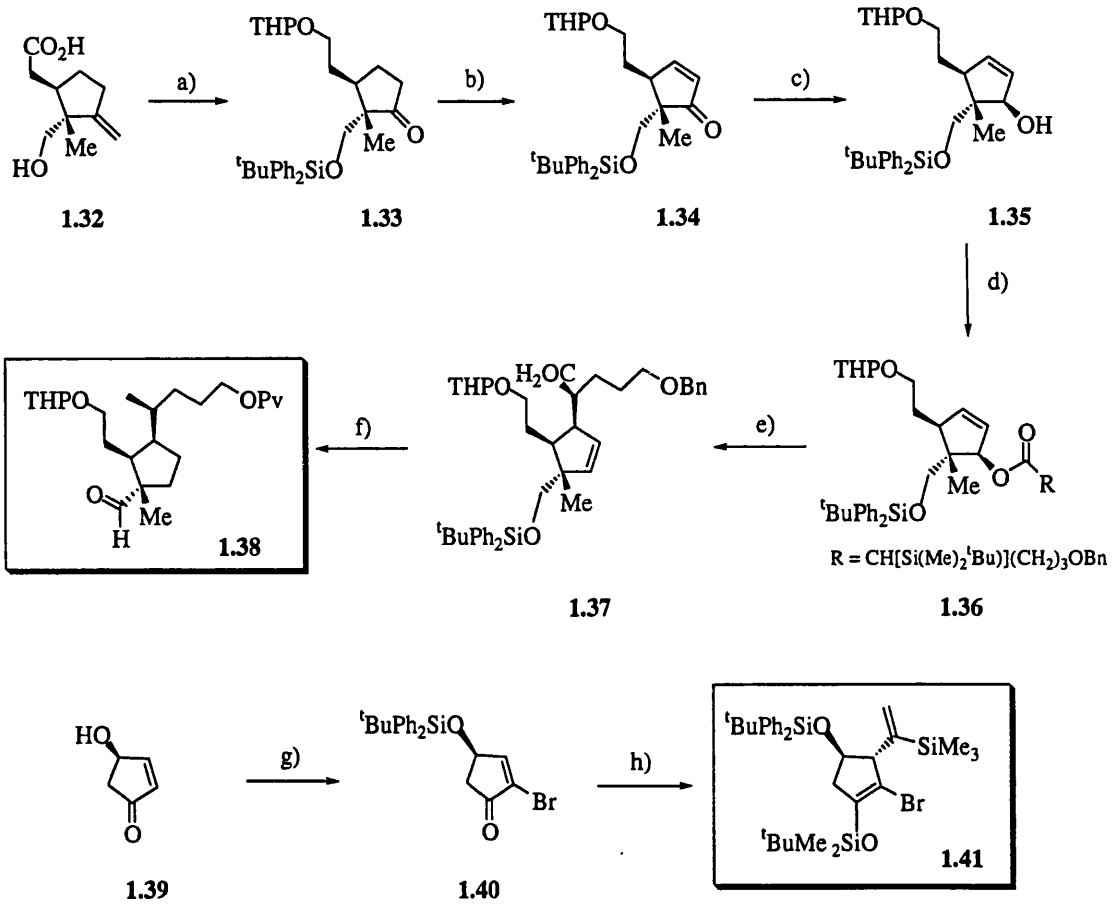


Scheme 1.3: Former total synthesis of cycloaraneosene, second part.

a) i: $CrCl_2$, DMF, ii: TMSCl, Pyr., 82 % over 2 steps; b) 190 °C, 12 h 100 %; c) i: KF, SiO_2, THF ii: KF, Fluoresil™, THF 84 %; d) $LiAlH_4$, THF, 96 %; e) DHP, PPTS, CH_2Cl_2, 95 %; f) H_2, Pd-C, EtOH, 97 %; g) Na, ^{t}BuOH/HMPA, *p*-TsOH, MeOH, 67 %; h) $(COCl)_2$-DMSO, Et_3N, 88 %; i) $TMSSO_3CF_3$, Et_3N, CH_2Cl_2, 71 %; j) $Pd(OAc)_2$, MeCN, 75 % k) i: DIBAL, toluene, ii: $^1O_2$ (Rose Bengal), PPh_3, 59 % over 2 steps; l) MsCl, Pyr., 76 % m) $CrCl_3$-$LiAlH_4$, DMF-THF, 78 % ; n) Ac_2O, Pyr., 96 % o) Li, ^{t}BuOH, liq.NH_3, 95 %.

[3+3] sigmatropic re-arrangment (Cope re-arrangment) provided bicyclic system **1.22** [7]. Deprotection, epimerisation and then reduction of the aldehyde moiety led to bicyclic system **1.23**. Careful stereocontrolled reduction of the remaining double bond with sodium in ^{t}Butyl alcohol/HMPA afforded dicyclopentane **1.25** as the major isomer. Swern oxidation followed by the formation of the di-silyl enol ether **1.27** and Saegusa oxidative re-arrangement [12] of the less hindered silyl enol moiety with $Pd(OAc)_2$ gave unsaturated aldehyde **1.28**. Reduction of the carbonyl and treatment with $^1O_2$ provided allylic alcohol **1.29**, which was in turn mesylated and finally cyclised in the presence of $CrCl_2$ to afford the tricyclic system **1.30**. Treatment with Ac_2O and reduction with Li in liquid NH_3 concluded the total synthesis of cycloaraneosene. This rather long strategy (over 30 steps) inconveniently includes a low-yielding resolution of the diol derivatives in the early stages and a lengthy functional group interconversion strategy before the formation of the central eight-membered ring. The same authors later proposed an alternative to the last steps of the synthesis [13]. This new synthetic route was not any shorter but introduced a powerful and versatile ring-closing method of the central eight-membered ring by an ene reaction mediated by $SnCl_4$. This key transformation was used again in the total synthesis of other related natural products, notably cyclotenol, hydrocycloaraneosene, (+)-fusicocca-2,10(14) diene [14], albolic acid and ceroplastol II [15].

Kishi *et al* also designed a similar convergent approach and have successfully applied their strategy to the total synthesis of ophiobolin C [16 17]. The synthetic strategy starts with the synthesis of the hydroxy-acid **1.32** in four steps from 3-*endo*-bromocamphor [18].

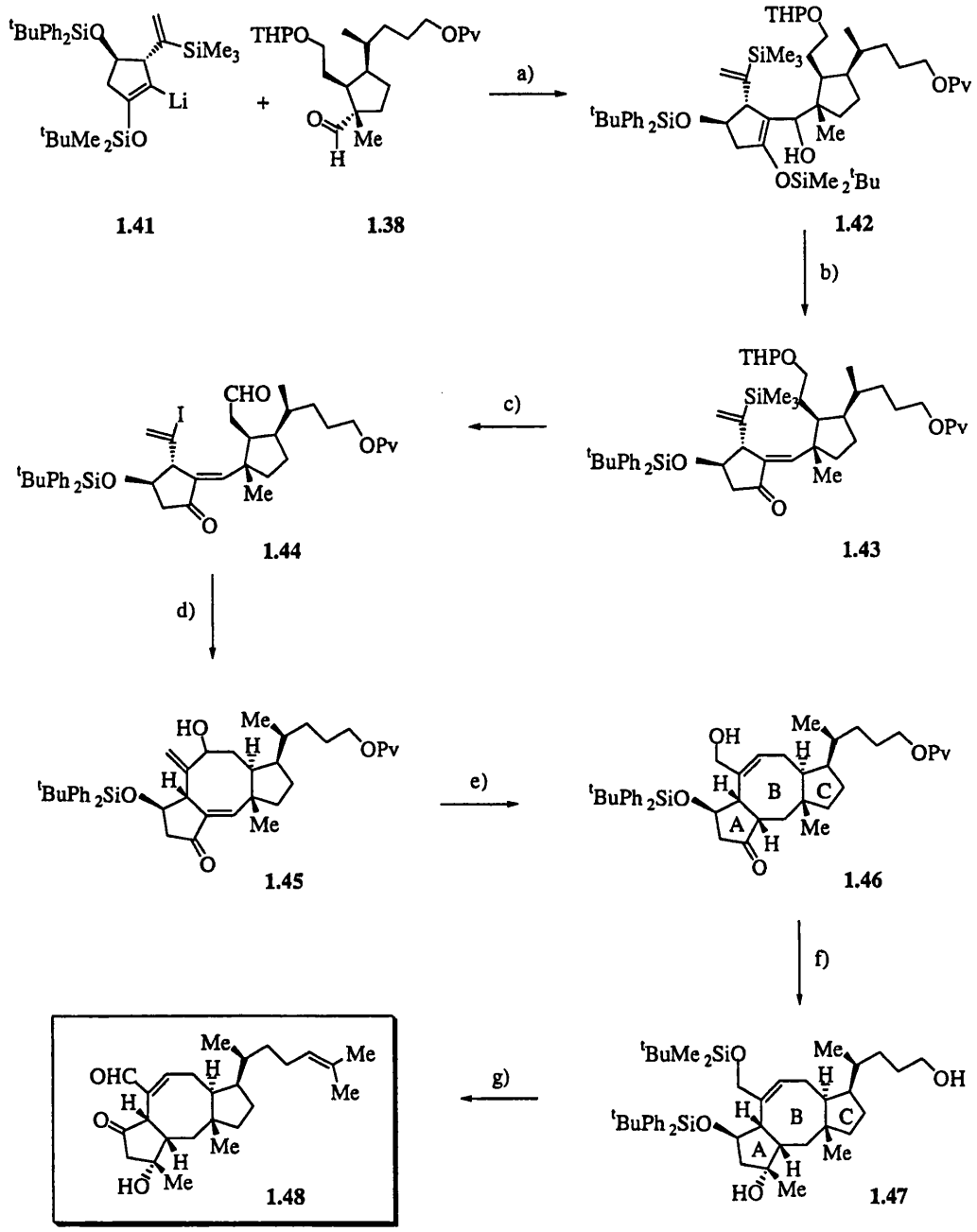


Scheme 1.4: Kishi's synthesis of the right and the left hand-side of ophiobolin C

a) i: ^{t}BuPh$_2$SiCl, AgNO$_3$, pyridine, ii: LiAlH$_4$; iii: DHP, PPTS CH_2Cl_2 iv: O_3, PPh_3 78 % over the last 4 steps b) Pd(OAc)$_2$, *p*-benzoquinone, CH_3CN 88 % c) $NaBH_4$, $CeCl_3$, MeOH, 81 %; d) i: ClOCCH[Si(Me)$_2$(^{t}Bu)](CH$_2$)$_3$OBn, KN(TMS)$_2$, THF e) i: xylene, 230 °C, ii: HCl, MeOH, Et_2O, 72 % over the last 3 steps; f) i: CH_2N_2, Et_2O, ii: LiAlH$_4$, Et_2O, iii: MsCl, Et_3N, CH_2Cl_2, iv: LiAlH$_4$, Et_2O, v: H_2, PtO_2, EtOAc, vi: H_2, Pd(OH)$_2$, EtOH, vii: PvCl, pyridine, viii: *n*Bu$_4$NF, DMF, 57 % over the last 8 steps, ix: Swern oxidation, no yield given; g) ^{t}BuPh$_2$SiCl, AgNO$_3$, Pyr. ii: Br_2, Et_3N, 77 % over the last 2 steps; h) [Me$_3$SiC(CH$_2$)CuC≡CPr]Li, ii: ^{t}BuMe$_2$SiOTf, 86 %.

Then, protection of the secondary alcohol (with concomitant esterification of the acid moiety) followed by sequential reduction of the resulting ester and protection of the alcohol with DHP provided the protected diol **1.33** [17]. The exocyclic double bond was ozonolysed and the resulting cyclopentanone intermediate was transformed into

cyclopentenone **1.34** by the method of Saegusa [12]. Luche reduction [19] favoured allylic alcohol **1.35** (3:1 ratio) and subsequent O-acylation afforded ester **1.36**. Tandem Brook [20] and Claisen rearrangement gave the carboxylic acid **1.37**. After esterification the acid was reduced to the alcohol, which was then mesylated and further reduced. The double bond was also reduced and the benzyl-protecting group cleaved by hydrogenation. The resulting primary alcohol was protected with pivaloyl chloride and the silylated alcohol was revealed and oxidised to generate aldehyde **1.38**, the right hand side of ophiobolin M. The left hand side five-membered ring **1.41** was prepared from (*R*)-4-hydroxycyclopentenone **1.39** following a four-step procedure [17]. Protection of the alcohol followed by a bromination-elimination sequence afforded α-brominated enone **1.40**. Diastereoselective 1,4-addition with the appropriate organocuprate and *in situ* trapping of the resulting enolate provided silyl enol ether **1.41**. The functionalised five-membered rings were then coupled together *via* the condensation of lithiated **1.41** on the aldehyde moiety of **1.38** [16]:



Scheme 1.5: Completion of the total synthesis of ophiobolin C

a) Et_2O, 85 %; b) i: 48 % aqueous HF-THF, c) i: ICl, nBu$_4$NF, CH_2Cl_2, ii: p-TsOH, CH_2Cl_2, MeOH, iii: Swern oxidation, 52 % over the last 4 steps; d) $Ni^{(II)}/Cr^{(II)}$, DMSO-DMS, 73 %; e) i: ^{t}BuOOH, $VO(acac)_2$, benzene, ii: 4-MeC_6H_4OC(S)Cl, Pyr., DMAP, CH_2Cl_2, iii: nBu$_3$SnH, AIBN, benzene, 52 % over the last 4 steps f) i: ^{t}Bu(Me)$_2$SiCl, imidazole, DMF, ii: MeMgBr, Et_2O, 68 % over 2 steps; g) i: Swern oxidation, ii: $(Me)_2C{=}P(Ph)_3$, THF, iii: nBu$_4$NF, THF, iv: Swern oxidation, 46 % over the last 4 steps.

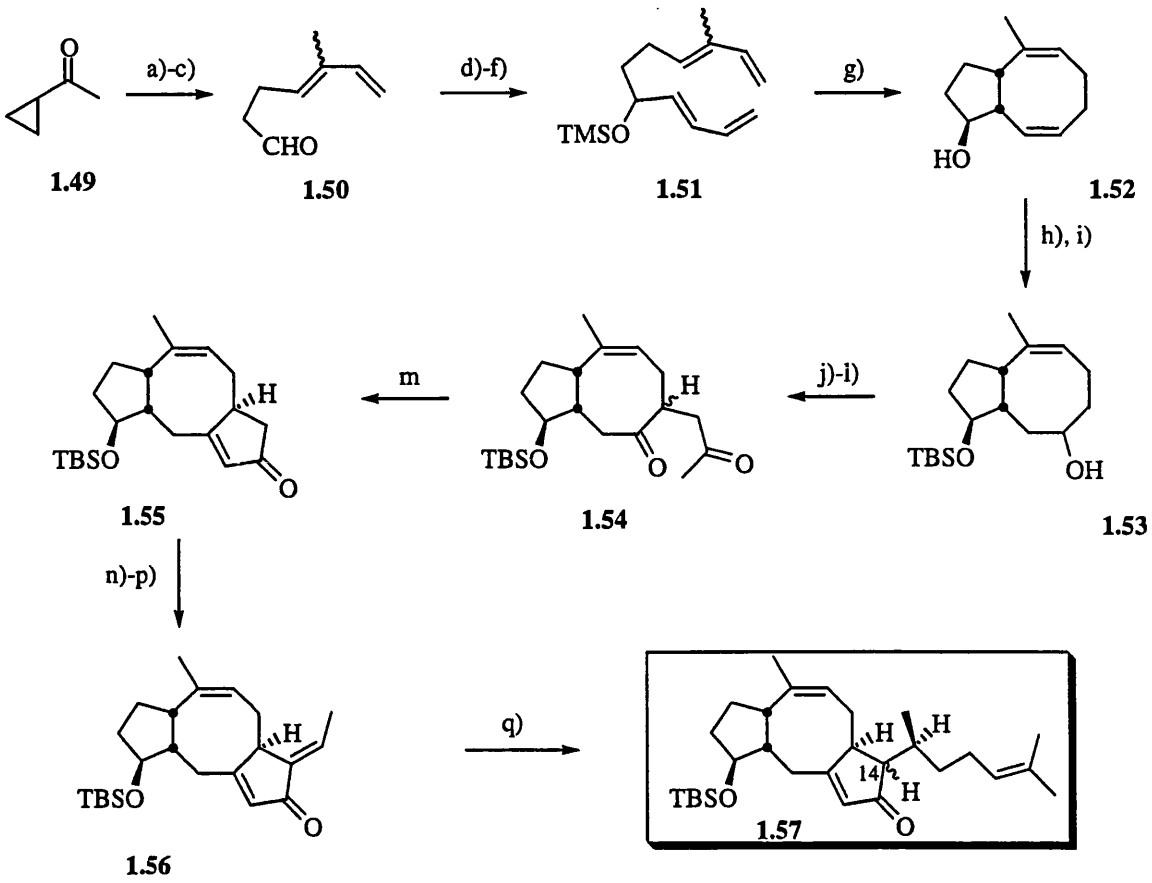
The silyl enol ether **1.40** was hydrolysed to afford the *E*-enone and vinyl iodide **1.43** after iododesylilation. Deprotection and subsequent oxidation of the resulting alcohol provided the key precursor vinyl iodide aldehyde **1.44** which was in turn cyclised *via* an intramolecular $Ni^{(II)}/Cr^{(II)}$ mediated coupling reaction. The resulting tricyclic intermediate **1.45** was transformed into allylic alcohol **1.46** following a three-step procedure described by Barton and Motherwell [21] (concomitantly the enone double bond was reduced and reasonable diastereocontrol was achieved at the ring junction A-B). The resulting alcohol was protected; the ketone moiety reacted with MeMgBr to afford nearly exclusively **1.47**. Sequential cleavage of the pivaloyl group, Swern oxidation, Wittig reaction and deprotection provided Ophiobolin C, **1.48** in over 30 steps. It is, to date, the only total synthesis of an ophiobolane.

On the same theme, the convergent approach to the core of ceroplastols developed by Snider and co-workers is also noteworthy [22].

1.22 *[4+4] Cycloadditions*

Another approach relies on a [4+4] intramolecular addition in order to construct the central eight-membered ring. Such a strategy is divergent and requires the synthesis of an adequate precursor.

Wender and co-workers first reported a nickel catalysed [4+4] cyclisation as part of their study towards the synthesis of the dicyclopenta[a,d] cyclooctene system [23].



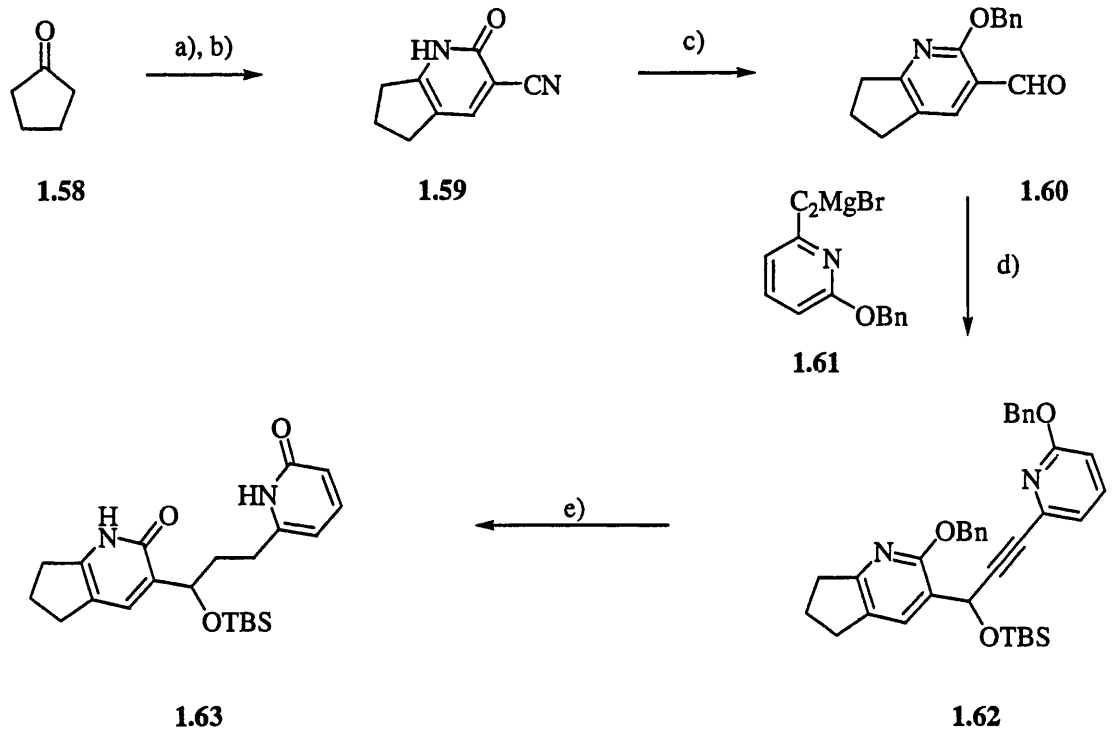
Scheme **1.6**: Wender's approach to the [5-8-5] tricyclic system

a) H_2C=CHMgBr, then HBr, 70 %; b) NaCN, 98 %, c) DIBAL, 72 %, d) LiC≡CCH=CH_2, 99 %; e) Red-Al, 91 %; f) TMS-imid, 99 %; g) $Ni(COD)_2$, PPh_3, nBu_4NF, 60%; h) TBSCl, imidazole, 99 %; i) 9-BBN, H_2O_2, NaOH, 86 %; j) PCC, 92 %; k) KHMDS, BEt_3 then CH_2=$CHCH_2I$; l) $PdCl_2$, H_2O, O_2, 88 % for 2 steps; m) 1N KOH-EtOH, 85 %; n) KHMDS, LiBr, CH_3CHO, 86 %; o) MsCl, DMAP, p) DMAP 68 % for 2 steps; q) $(CH_3)_2C$=$CHCH_2CH_2MgBr$, CuBr.DMS, 97 %.

Diene **1.50** was prepared in three steps from commercially available cyclopropyl methyl ketone following a method previously described in the literature [24]. Conversion of the unsaturated aldehyde **1.50** into cycloaddition precursor **1.51** was accomplished by condensation with LiC≡CCH=CH_2, followed by *E*-selective reduction of the resultant alkyne with Red-Al and silylation of the alcohol functionality. Then, treatment with a catalytic amount of $Ni(COD)_2$ and triphenylphosphine, followed by deprotection of the alcohol moiety, provided the [5-

8] bicyclic system **1.52** in 60 % yield and good stereocontrol (only 8 % of other isomers were formed). The second fused five-membered ring was introduced through a five-step annulation sequence. The least substituted double bond was chemoselectively and regioselectively hydroborated with 9-BBN. The resulting alcohol **1.53** was then oxidised with PCC and followed by alkylation with KHMDS and allyl iodide. Subsequent Wacker oxidation of the allyl moiety followed by treatment with KOH afforded enone **1.55**. After alkylation with acetaldehyde, the resulting alcohol was mesylated and eliminated to provide exocyclic alkene **1.56**. Copper-catalysed 1,4-addition of the Grignard reagent derived from 5-bromo-2-methyl-2-pentene led to a diastereoisomeric 1:1 mixture of isomers **1.57**. The entire process represents a short synthetic sequence towards the synthesis of [5-8-5] tricyclic systems, based on a rapid construction of the [5-8] bicyclic system from a readily available precursor (five synthetic steps only). Although the stereochemistry at C_{14} could not be controlled, epimerisation was also effectively achieved. Unfortunately, no further development towards the total synthesis of a natural product has been reported.

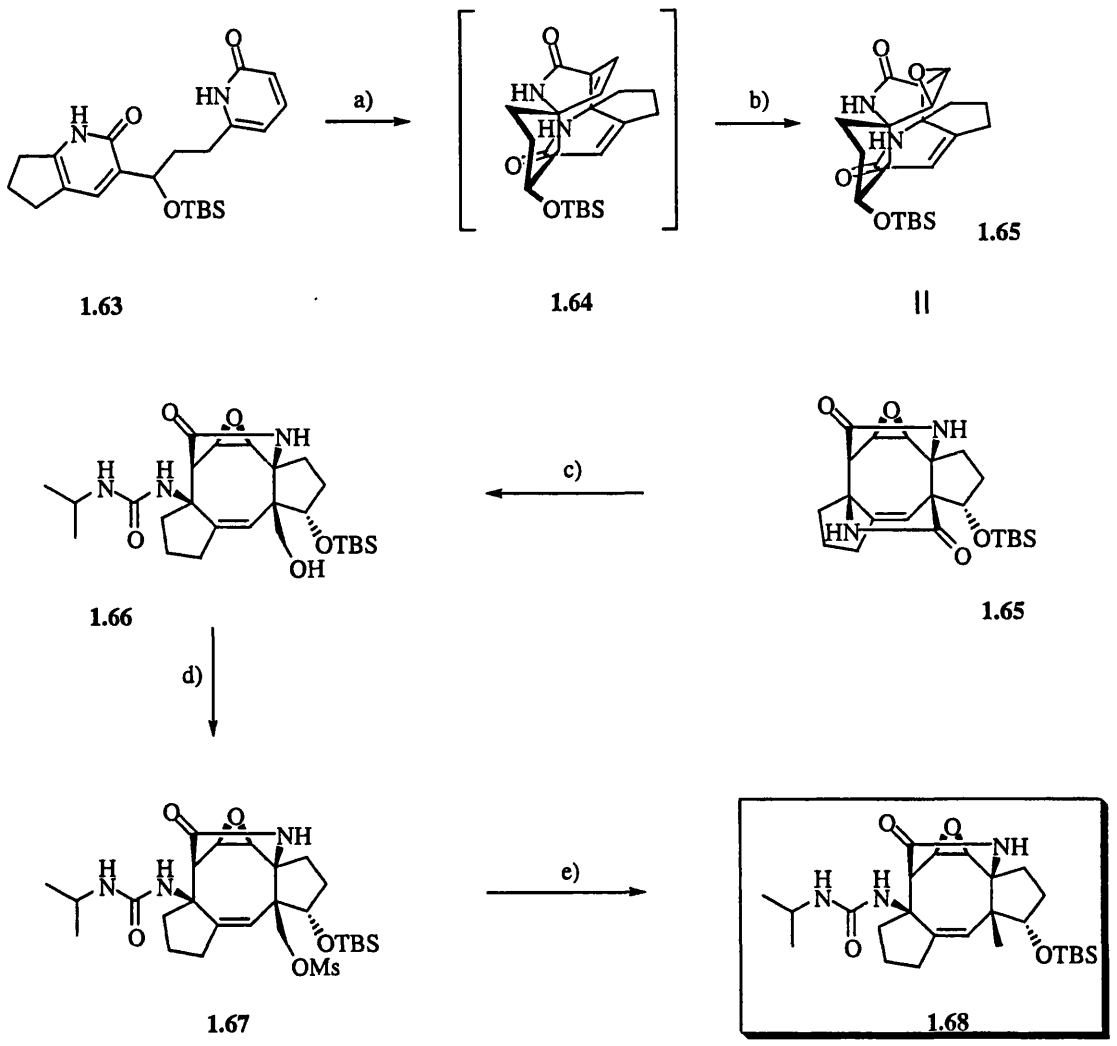
More recently, Mc Gee *et al* included a [4+4] cycloaddition in their approach towards [5-8-5] core systems [25] [26]. However, this time the key cycloaddition involves a photochemical process.



Scheme 1.7: Synthesis of cyclopentane-annulated bis-2-pyridones **1.63**.

a) Na, HCO_2Et, 63 %; b) $NC(CH)_2CONH_2$, 79 %; c) i: BnBr, Ag_2CO_3, 95 % ii: DIBAL, 92 %; d) i: **1.61**, 86%, ii: TBSCl, 87 %; e) H_2, Pd-C, 63 %.

Bis-pyridone **1.63** was the key [4+4] cycloaddition precursor and was synthesised in seven steps from cyclopentanone. Firstly, pyridinone **1.59** was obtained in 2 steps according to a previously reported procedure [27]. Benzylation of the amide moiety and subsequent reduction of the nitrile functionality with DIBAL led to aldehyde **1.60**. Coupling with Grignard reagent **1.61** followed by derivatisation with TBSCl gave silyl ether **1.62**. Hydrogenation with palladium on carbon produced key intermediate **1.63**. The [4+4] photocycloaddition was then performed in toluene at 0 °C:



Scheme 1.8: Mc Gee's synthetic approach (second part)

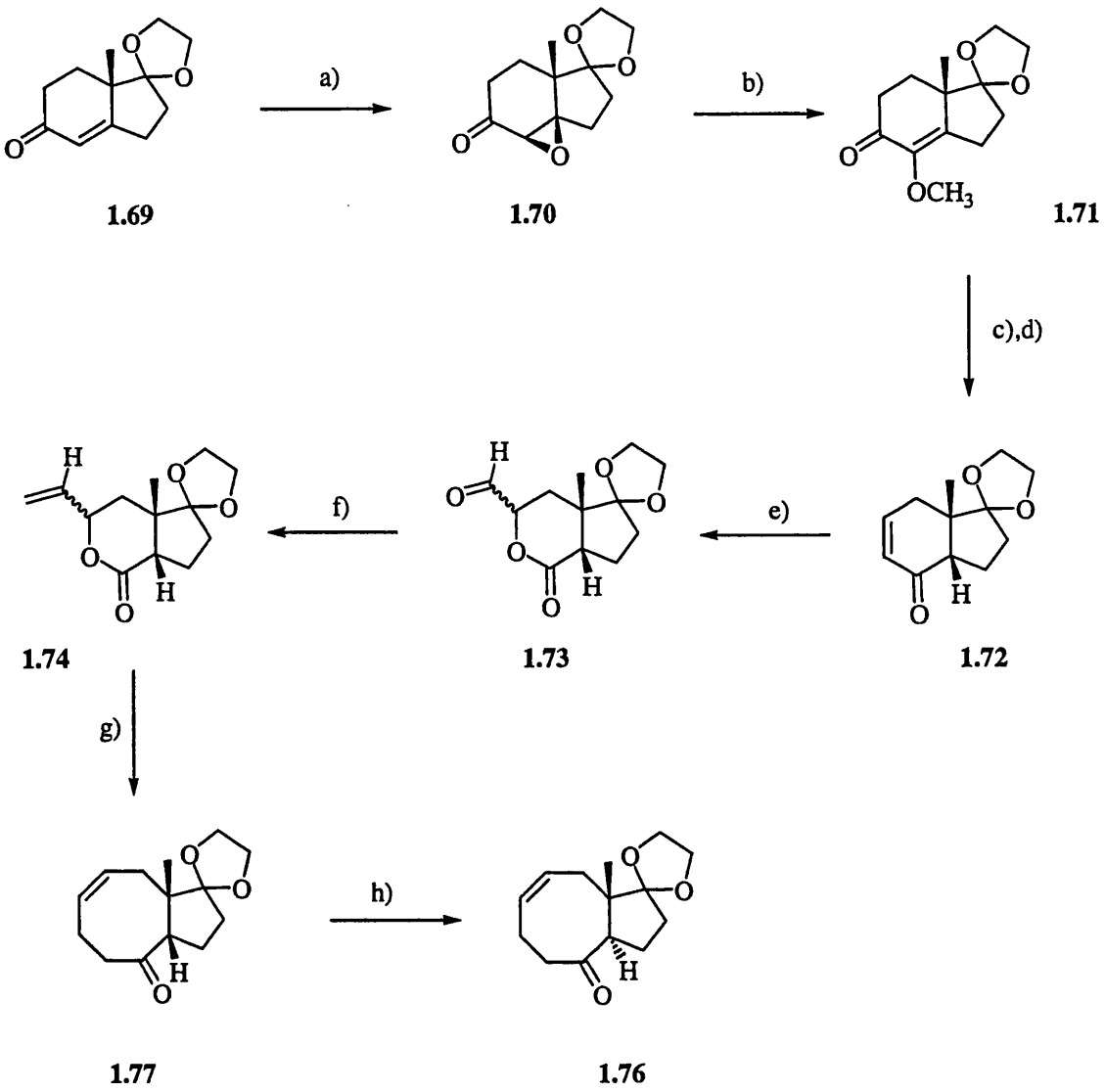
a) hν, toluene; b) dimethyldioxirane, 84 % over 2 steps c) i: *i*PrNCO, NaH , 76 %, ii: $LiBH_4$, 64 %; d) MsCl, 76 %; e) LiI, Zn, DMF, 90 %.

Intermediate **1.64** was trapped *in situ* with dimethyldioxirane to afford the photoadduct **1.65**. Selective protection of the less hindered nitrogen amide followed by careful and selective reduction with $LiBH_4$ of the activated carbonyl amide afforded alcohol **1.66** which was then further mesylated to the activated alcohol **1.67**. Finally, treatment with zinc metal and LiI in DMF provided the pentacyclic system **1.68**. This last approach includes the first *cis*-selective pyridinone [4+4] photocycloaddition as well as the first reduction of an amide to a methyl group in a

polycyclic pyridinone photoproduct. However, due to the rigidity of the bridged cyclooctane **1.68**, cleavage of the remaining amide bond could not be performed and no further transformation towards the synthesis of a fusicoccane or any [5-8-5] tricyclic system could be achieved.

1.23 *Ring-expansion of a medium-size ring*

A third entry to the [5-8-5] tricyclic ring system consists of a ring-expansion of a more accessible medium-size ring. Notably, Paquette *et al* applied this strategy to the total synthesis of ceroplastol I *via* a crucial [3+3] sigmatropic re-arrangement [28].

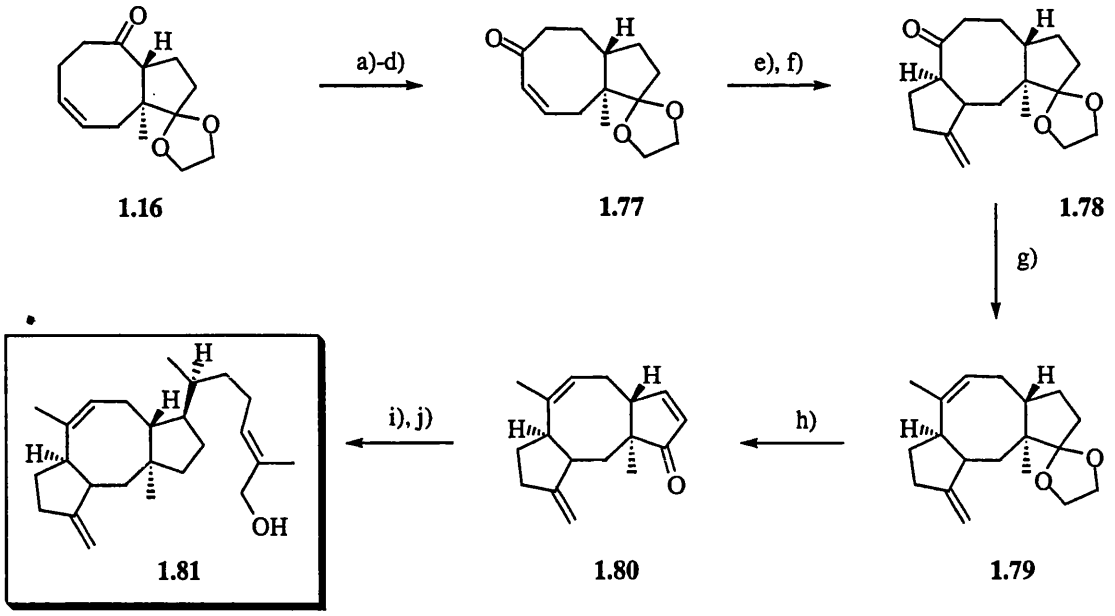


Scheme 1.9: Paquette's ceroplastol I synthesis: Claisen re-arrangement applied to a ring-expansion

a) i: $NaBH_4$, $CeCl_3$, ii: *m*CPBA, iii: PDC, 57 % over 3 steps; b) $NaOCH_3$, CH_3OH, 65 % c) i: $TsNHNH_2$, CH_3OH, ii: CH_3Li, THF, Et_2O, d) i: NH_4Cl, H_2O, ii: HOAc, H_2O, 62 % over the last 4 steps; e) i: *m*CPBA, $NaHCO_3$, CH_2Cl_2, ii: heat, benzene, 55 % over 2 steps; f) $Ph_3PCH_3^+Br^-$, $KN(SiMe_3)_3$, THF 61 %; g) i: $Cp_2Ti(Cl)(CH_2)Al(CH_3)_2$, THF, Pyr., ii: heat in KOH coated tube, 61 % over 2 steps; h) K_2CO_3, CH_3OH, heat, 93 %.

The starting keto-acetal **1.69** was available by mono-ketalisation of the optically pure diketone precursor [29]. Sequential Luche reduction [19] of the unsaturated carbonyl,

epoxidation with *m*CPBA and oxidation with PDC led to keto-epoxide **1.70**. Opening of the epoxide with sodium methoxide and subsequent dehydration afforded keto-enol ether **1.71**. Shapiro reaction followed by acidic hydrolysis of the enol ether produced enone **1.72**, which in turn was transformed into ring-expanded lactone **1.73** *via* an epoxy-lactone intermediate. The resulting aldehyde was treated with the appropriate phosphorus ylide and the resulting lactone **1.74** was treated with Tebbe 's reagent to undergo a [3+3] Claisen re-arrangement and a concomitant ring-expansion. The resulting *cis*-fused cyclooctenone **1.75** was epimerised to the more favoured *trans* isomer **1.76** under basic conditions.



Scheme 1.10: Last steps of Paquette's ceroplastol I synthesis.

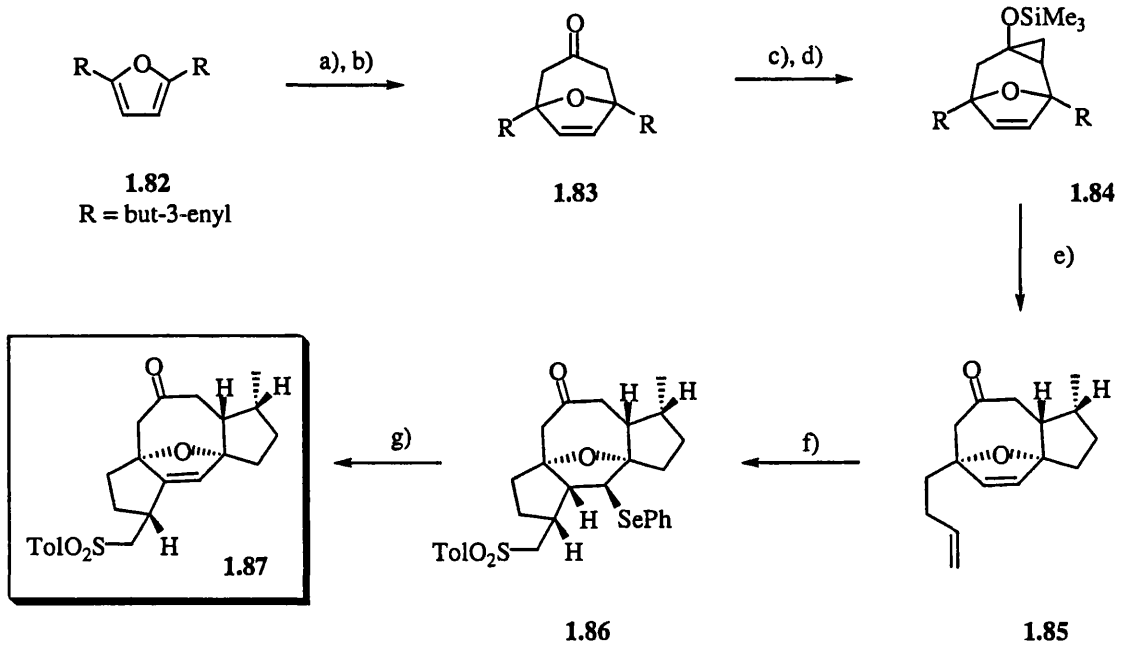
a) i: $LiAlH_4$; ii: *n*BuLi, $ClP(O)(NMe_2)_2$; b) Li, $C_2H_5NH_2$, *t*BuOH, Et_2O, 73 % over 3 steps; c) SeO_2, KH_2PO_4, toluene, 61 %; d) PDC, 80 %; e) i: $(ClCH_2CH_2C{=}CH_2)_2CuLi$, THF 78 % f) KH, THF, 90 %; g) i: $KN(SiMe_3)_2$, Tf_2NPh, ii: $(CH_3)_2CuLi$, THF, 68 % over 2 steps; h) TsOH, acetone, 84 %; h) $LiN(SiMe_3)_2$, $(CH_3)_3SiCl$; $Pd(OAc)_2$, CH_3CN, 40 %; i) $TBSOCH_2(CH_3)C{=}CH(CH_2)_2CH(Cl)CH_3$, Mg, $CuBr.Me_2S$, HMPA, THF, Me_3SiCl, 47 %; j) i: $TsNHNH_2$, $(COOH)_2$, C_2H_5OH, ii: $NaBH_3CN$, $ZnCl_2$, CH_3OH, heat, 55 % over both steps.

A four-step sequence was necessary to enable the 1,3-carbonyl shift and to generate α,β-unsaturated enone **1.77**. Subsequent copper mediated 1,4-addition and intramolecular cyclisation of the resulting addition product produced the [5-8-5] tricyclic intermediate **1.78**. The kinetic enolate of **1.78** was converted to its triflate derivative, which was coupled with dimethylcuprate to afford tricyclic ketal **1.79**. Deprotection, formation of the silyl enol intermediate and subsequent oxidation according to Saegusa's method [12] provided enone **1.80**. Finally, another copper mediated 1,4-addition followed by complete reduction of the carbonyl moiety and deprotection of the terminal alcohol completed a 24 linear step synthesis of

ceroplastol I. The same authors also used a similar strategy for the construction of the ophiobolane [5-8-5] core system [30].

In 1994 Schreiber and co-workers took advantage of the key [3+3] sigmatropic rearrangement in their synthesis of a closely related [5-5-8-5] quadracyclic natural product, epoxydictymene [31]. Rigby *et al* also adapted this popular type of ring-expansion to their approach of [5-8-5] tricyclic system [32].

More recently, Simpkins *et al* reported a concise entry to highly functionalised [5-8-5] tricyclic systems *via* a new type of ring expansion [33].



Scheme 1.11: Simpkin's synthetic approach.

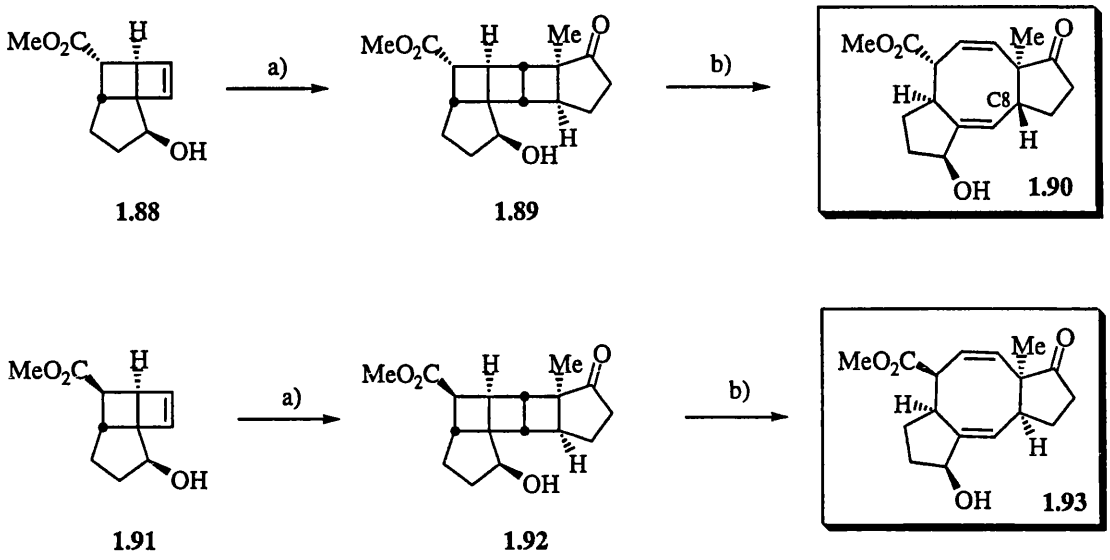
a) Trichloroacetone, TFP, NaH; b) Zn/CuI, MeOH, benzene, 83 % over 2 steps; c) LDA, Me_3SiCl; d) Et_2Zn, CH_2I_2, Et_2O, 79 % over 2 steps; e) $Fe(NO_3)_3$, DMF, cyclohexadiene, 66 %; f) $PhSeSO_2Tol$, AIBN, benzene, 72 %; g) H_2O_2, THF, 57 %.

The synthesis commences with a [4+3] cycloaddition of readily available substituted furan **1.82** with trichloroacetone under Föhlisch conditions [34] to afford the

symmetric bicyclic ketone **1.83**. The corresponding silyl enol ether was cyclopropanated and provided trimethylsilyloxycyclopropane **1.84**. A modified Saegusa reaction [35] [36] [37] to cleave regioselectively the cyclopropane moiety resulted in ring-expansion and subsequent annelation (bicyclic system **1.85**); the entire process was diastereoselective. Radical cyclisation with AIBN and $PhSeSO_2Tol$ led to the oxa-bridged [5-8-5] tricyclic system **1.86**. Finally, treatment with H_2O_2 afforded alkene **1.87**. Further transformation towards the total synthesis of a natural product has yet to be reported; notably, the authors also comment on the unusual lack of reactivity of the bridged oxygen. However this strategy represents a concise diastereocontroled entry to highly functionalised [5-8-5] tricyclic systems. Furthermore, the authors believe that key intermediate **1.83** could be desymmetrised with a chiral base: the same strategy would then provide an enantioselective approach to functionalised [5-8-5] tricyclic system.

1.24 *Ring fragmentation of a polycyclic system*

Ring-fragmentation of a polycyclic system has also been investigated and several groups have reported efficient routes towards the [5-8-5] ring system. Among them, Snapper *et al.* reported the efficient fragmentation of a [5-4-4-4-5] ring system into a functionalised [5-8-5] framework [38].

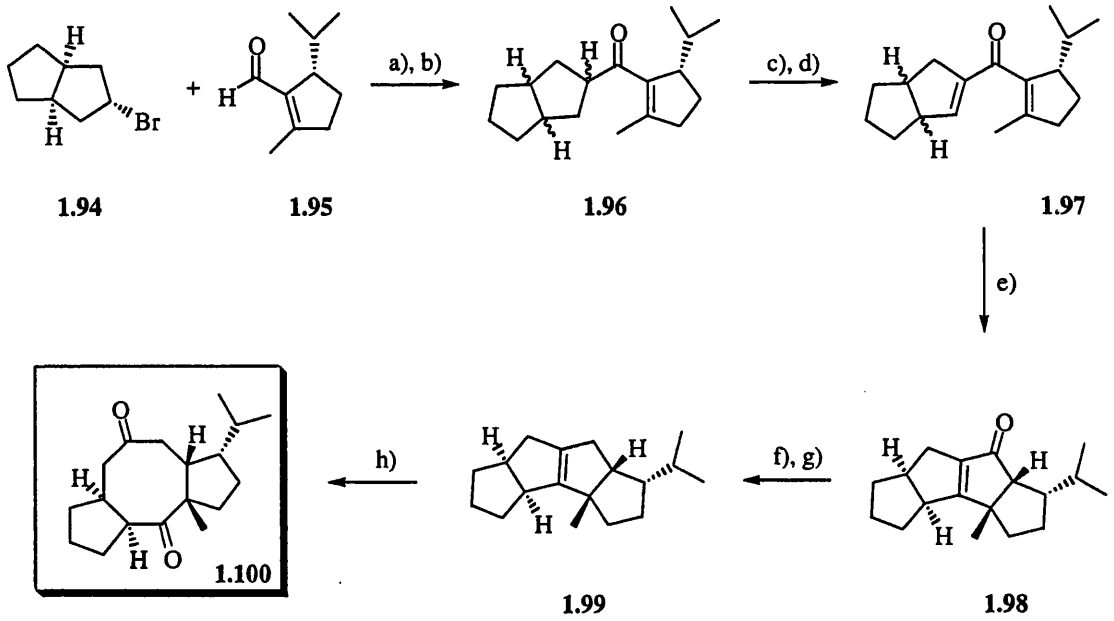


Scheme 1.12: Snapper's entry to functionalised [5-8-5] tricyclic systems

a) 2-methylcyclopentenone, pentane, hv, 52 % in both cases; b) heat (200 –240 °C), benzene, 68 % for F3, 70 % for F6.

Firstly, both isomers **1.88** and **1.91** were obtained in one step *via* the intramolecular cyclisation of the corresponding tricarbonyl(η^4-cyclobutadiene)iron complex [39]. Then, a [2+2] photocycloaddition with 2-methyl cyclopentenone afforded the pentacyclic system as a single isomer in each case [38] [40]. Thermal fragmentation of the photoadducts **1.89** and **1.92** provided the [5-8-5] tricyclic systems **1.90** and **1.93**, of which the stereochemistry could be predicted from their respective precursor (aside from the unexpected epimerisation at C8 which is still under investigation [38]). To date, no further development of this stereoselective and rapid entry (four steps from the suitable tricarbonyl(η^4-cyclobutadiene)iron complex) has been reported by the authors.

Metha *et al.* ring-fragmented a [5-5-5-5] system into a [5-8-5] tricyclic system [41].



Scheme 1.13: Metha's approach; the fragmentation of a [5-5-5-5] polycyclic system

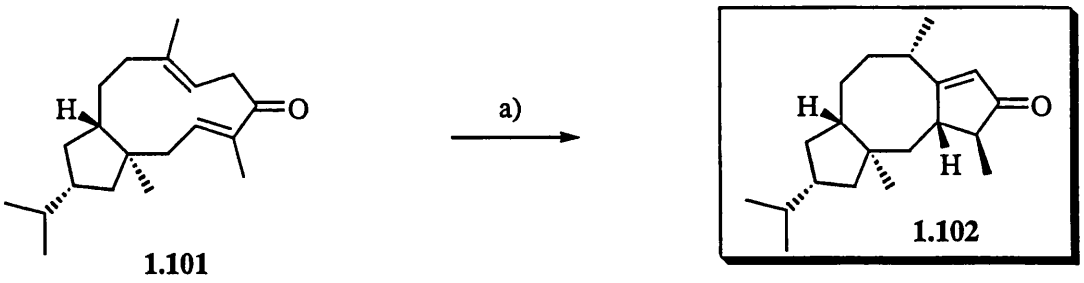
a) Li, THF, ultrasound, 40 %; b) $BaMnO_4$, CH_2Cl_2, 55 %, c) 2,4,4,6-tetrabromocyclohexa-2,5-dienone; d) Li_2CO_3-LiBr, DMF, 80 °C, 26 % over 2 steps; e) *p*-$MeC_6H_4SO_3H$, toluene, 110 °C, 20 %; f) $HSCH_2CH_2SH$, *p*-$MeC_6H_4SO_3H$, benzene; g) Na, liq. NH_3; h) RuO_2, $NaIO_4$, CCl_4, MeCN, H_2O, 82 % over the last 3 steps.

Their approach commences with the condensation of lithiated exo-3-bromobicyclo[3.3.0] octane **1.94** with the unsaturated aldehyde **1.95** which is available in four steps from limonene [42]. The resulting alcohol was oxidised to the unsaturated ketone **1.96**, which was in turn brominated and subjected to elimination conditions to yield dienone **1.97**. Nazarov type cyclisation provided the key tetracyclic enone **1.98**. Complete reduction of the carbonyl moiety provided quadracyclic compound **1.99**. The central eight-membered ring was then generated upon oxidation with $RuO_2/NaIO_4$ to afford the [5-8-5] tricyclic dione **1.100**. However, this synthetic approach has yet to be applied to the synthesis of a natural

product and generally suffers from two very low-yielding steps, notably the key Nazarov cyclisation (20 % yield). Finally, before Paquette and co-workers, Boeckman achieved the total synthesis of ceroplastol I *via* the fragmentation of a [5-5-5-5] polycyclic system [43].

1.25 *Ring contraction of a macrocyclic system*

Coleman *et al* described a fifth and rather unique entry to the [5-8-5] carbon skeleton [44]. Their approach relies on a key ring-contraction step and is perhaps specific to a single natural products family, the fusicoccane.



1.101 **1.102**

Scheme 1.14: Coleman's ring-contraction

a) $BF_3.Et_2O$, CH_2Cl_2, 30 %.

In fact, this synthetic strategy re-enacted the biogenetic pathway described earlier: dolabelladienes are believed to be the biogenetic precursor to fusicoccane *via* an acid–induced cyclisation (see **Scheme 1.1**). The authors took advantage of this simple observation and cyclised dolabelladienone **1.101** (which had previously been the object of a 12 step total synthesis [45]) with Lewis acids, amongst which $BF_3.Et_2O$ afforded the best results [44]. This method provides immediate access to the

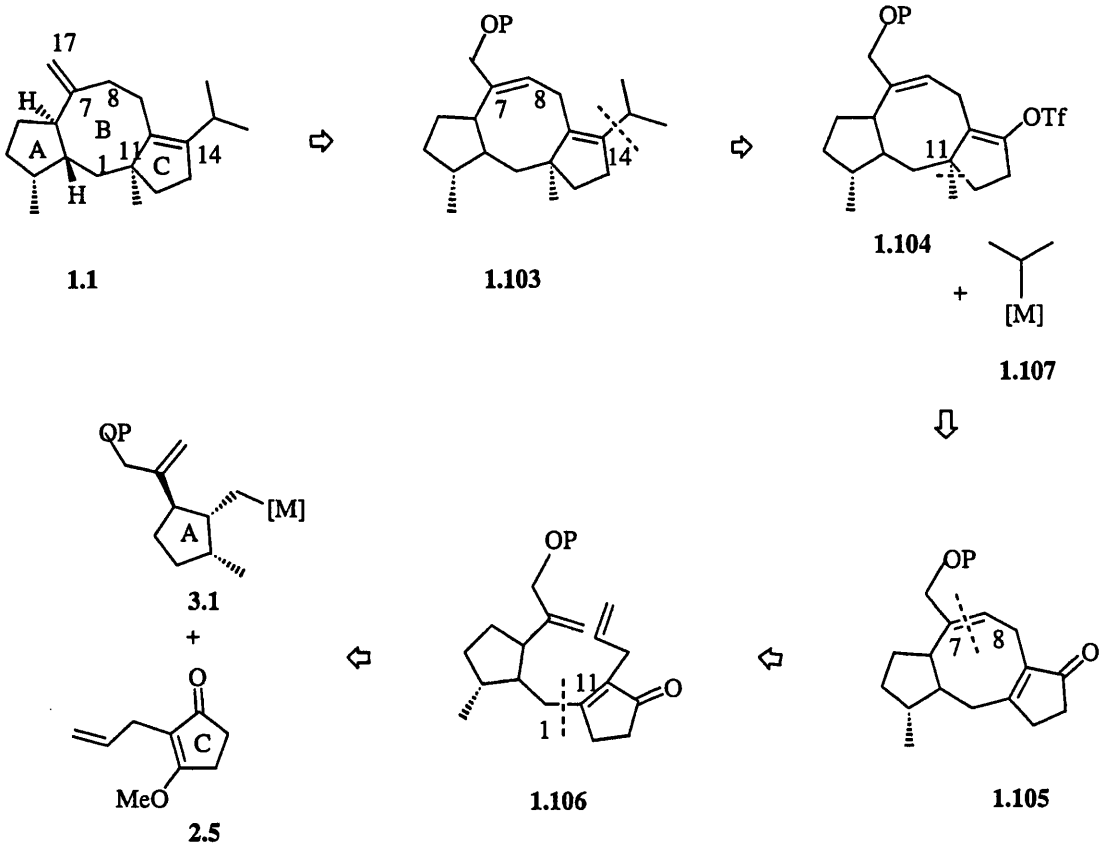
fusicoccane skeleton **1.102** but has yet to be employed in the total synthesis of a natural product.

1.3 Synthetic strategy

Our strategy towards the total synthesis of cycloaraneosene relies on a convergent approach.

Several years ago, Takeshita and co-workers proved the applicability of such an approach to cycloaraneosene [7] in particular but also to other [5-8-5] tricyclic systems [14] [15]. On the same theme, Kishi *et al* elaborated the only methods towards the synthesis of an ophiobolin [16]. As opposed to a convergent approach, numerous strategies, which relied on a key transformation derived from methodological study, have shown limited success. Such strategies generally offered a rapid entry to the tricyclic framework but their lack of adaptability often led to insurmountable synthetic difficulties at the latter stages of the synthesis. As outlined earlier, the photocycloaddition of Mc Gee and co-workers was defeated when a surprisingly unreactive amide functionality could not be further transformed [25]. Simpkins *et al* encountered the lack of reactivity of a bridged-oxygen and, to date, their unique strategy has failed to lead to the total synthesis of any natural product [33]. Similarly, Wender's [4+4] cycloaddition [23], Snapper's [38] and Metha's ring-contraction [41] methods have not yet met with success.

It is hoped that a tailored convergent approach could provide a new and concise entry to the total synthesis of cycloaraneosene. Our retrosynthetic analysis is detailed below:



Where M = Metal , P= protecting group

Scheme 1.15: Retrosynthetic analysis

The last transformation relies on a double bond transposition performed on the tricyclic intermediate **1.103** (C_7-C_8 to C_7-C_{17}). Disconnection at C_{14} reveals the possibility of a metal-mediated coupling reaction between vinyl triflate **1.104** and the metallated side-chain **1.107**. Further disconnection at the quaternary carbon centre C_{11} leads to enone **1.105**. In the synthetic direction, the methyl group would be introduced *via* a 1,4-addition. Disconnecting the central eight-membered ring along the C_7-C_8 double bond provides the bicyclic trialkene **1.106**, precursor to the ring-closing metathesis reaction. Finally, disconnection at C_1-C_{11} leads to pre-formed rings A **3.1** and ring C **2.5**. A metal mediated reaction would couple ring A onto ring C.

Stereochemical aspects will be discussed in the individual chapters. The synthesis of ring A **3.1** and ring C **2.5** will be investigated separately.

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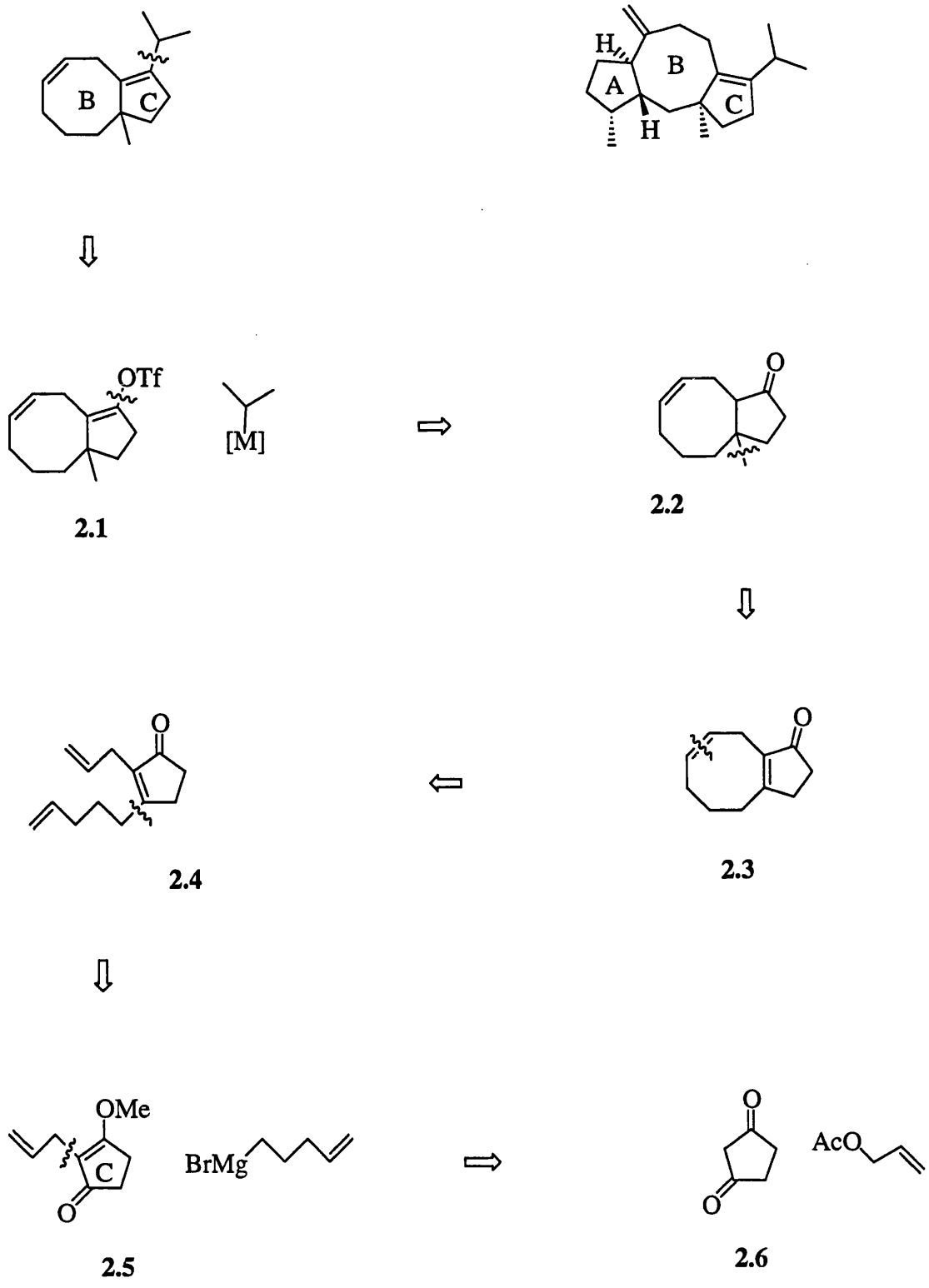
Chapter 2:

Synthesis of Ring C and Model Study on the B-C Ring System

2.1 Retrosynthetic analysis

If ring A is viewed as an exocyclic group attached to the [5-8] bicyclic system B-C then model studies can be conducted on this bicyclic system. Furthermore, in our overall strategy towards cycloaraneosene (**Scheme 2.1**), the ring-closing metathesis reaction as well as the functionalisation of the right-hand side of the molecule (ring C) is planned in the second half or at even later stages of the synthetic pathway. It is necessary to assess the feasibility of these late transformations on a more readily accessible model bicyclic system B-C in order to validate our overall synthetic strategy.

Our approach towards the synthesis of ring C and bicyclic system B-C is outlined in **Scheme 2.1**:



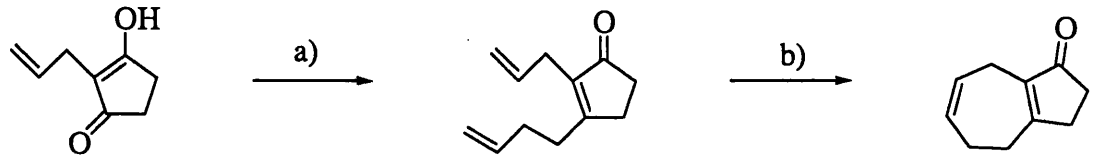
Scheme 2.1: Retrosynthetic analysis towards ring C and bicyclic system B-C.

The exocyclic isopropyl side-chain could be attached *via* an appropriate metal catalysed reaction, possibly involving commercially available isopropylmagnesium

chloride and vinyl triflate **2.1**. Vinyl triflate **2.1** can be further disconnected to bicyclic enone **2.2**. In a forward sense, the thermodynamic enolate could be trapped with a source of triflate such as 2-[*N,N-Bis*(trifluoromethylsulfonyl)amino]-5-chloropyridine. Introduction of the quaternary methyl group at the ring junction B-C would rely on a 1,4-addition involving a suitable organocuprate reagent reactive enough to perform a conjugate addition on β,β-disubstituted enone **2.3**.

Disconnecting the disubstituted double bond leads to triene **2.4**, precursor to the key ring-closing metathesis. Further disconnection of the pentenyl moiety gives ring C **2.5**. In the synthetic direction, the Grignard reagent obtained from commercially available bromopentene would be reacted with the carbonyl of ring C. Finally, methyl enol **2.5** could be obtained in two steps from commercially available 1,3-cyclopentadione **2.6** and allyl acetate.

Our synthetic approach to the ring system B-C is supported by earlier work reported by Blechert and co-workers [1]. A closely related triene system obtained from allylated cyclopentadione **2.7** was cyclised to a [5-7] bicyclic system *via* a ring-closing metathesis reaction:

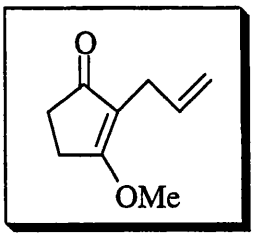


2.7 **2.8** **2.9**

Scheme 2.2: Blechert's [5-7] system

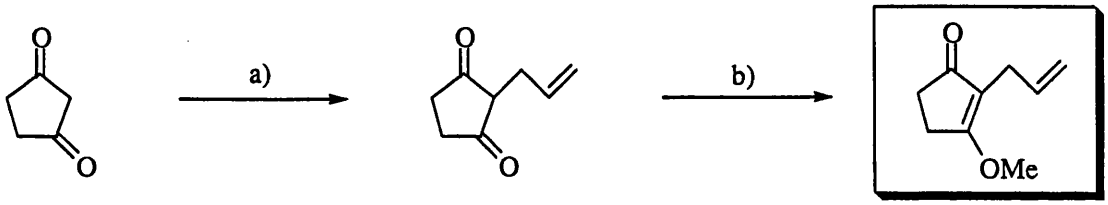
a) i: EtOH, HCl, 96 %, ii: butenylmagnesiumbromide, HCl, 49 %; b) Ru. Catalyst, 94 %.

2.2 Synthesis of ring C



2.5

The synthesis of the right-hand side of cycloaraneosene, ring C **2.5**, was achieved in two steps, starting from commercially available 1,3-cyclopentadione **2.6**:

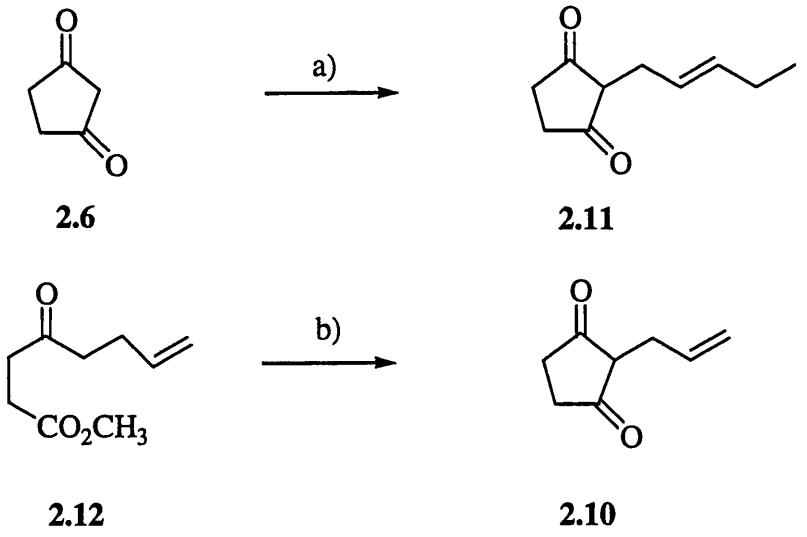


2.6 **2.10** **2.5**

Scheme 2.3: Synthesis of ring C

a) allyl acetate, $[Pd(C_3H_5)Cl]_2$, dppe, BSA, cat. NaOAc, THF, reflux, 24 h, 90 %; b) $(MeO)_3CH$, conc. H_2SO_4, MeOH, reflux, 1 h, 65 %.

Firstly, 1,3-cyclopentanedione **2.6** was allylated in good yield following a one-step palladium catalysed reaction. A precedented literature procedure for the synthesis of 2-allyl-1,3-cyclopentanedione **2.10** involved cyclisation of an acyclic precursor [2] and direct alkylations of 1,3-cyclopentanedione **2.6**, which gave low to moderate yields [3].



2.6 **2.11**

2.12 **2.10**

Scheme 2.4: Former allylations of 1,3-cyclopentanedione

a) $ClCH_2=CHC_2H_5$, KOH, H_2O, rt, 41 %; b) EtONa, toluene, HCl, 160 °C, 35 %.

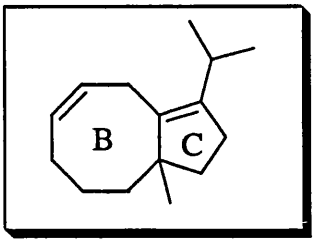
Competing O-alkylation limited the yield of allylated product **2.11** to 41 %, even when the reaction was conducted in strongly protonating solvents such as H_2O [3]. Alternatively, harsher conditions were required when using an acyclic keto ester precursor **2.12** and even lower yields (35 %) were obtained [2]

Proceeding *via* a Pd(0) catalysed allylic substitution [4] gave excellent yields of the allylated product in a single step. It is noteworthy that this transformation was also performed on a larger scale (up to 14 g of starting dione **2.6**) without affecting the yield of the reaction. ^{1}H NMR analysis in d^4-methanol showed the predominance of the enol form. The signal due to the allyl methylene appears as a doublet at 2.92 ppm. A broad singlet, partly overlapping with the terminal alkene proton signals at 5.10 ppm, most probably accounted for the enol proton. Interestingly, in the ^{13}C NMR spectrum, both alkyl methines seemed to give rise to a single carbon signal: their respective chemical shifts might be identical, due to the almost symmetric character of the molecule.

The allylated cyclopentanedione **2.10** was then converted into the corresponding methyl enol ether **2.5** in refluxing methanol in the presence of concentrated acid and trimethyl orthoformate [5]. Examination of the ^{1}H NMR spectrum revealed a signal caused by the resonance of the methyl protons (singlet at 3.96 ppm). In the ^{13}C NMR spectrum, every carbon gave rise to a distinct resonance signal: both methine carbons are now differentiated (24.6 ppm and 25.5 ppm).

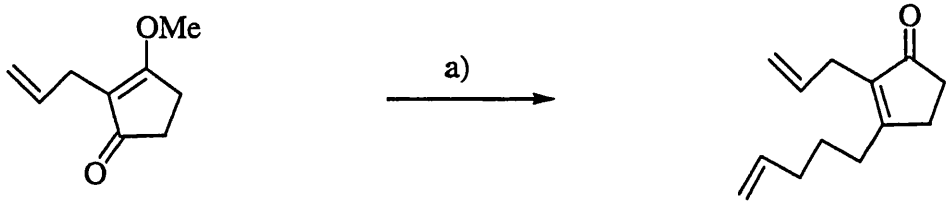
Methyl enol ether **2.5** proved to be moisture-sensitive and the aqueous work-up conditions sometimes resulted in its partial hydrolysis back to the allylated dione **2.10**. However, methyl enol **2.5** was stable enough to be purified by flash chromatography (basified SiO_2, Et_2O) to provide a yellow brown oil, which could be stored for several days under an inert atmosphere of nitrogen at temperatures below 5 °C.

2.3 Studies towards the bicyclic system B-C



2.31 *Synthesis of triene 2.4, the ring-closing metathesis precursor.*

The methyl enol ether **2.5** was then reacted with the Grignard reagent derived from pentenyl bromide (**Scheme 2.5**):



2.5 **2.4**

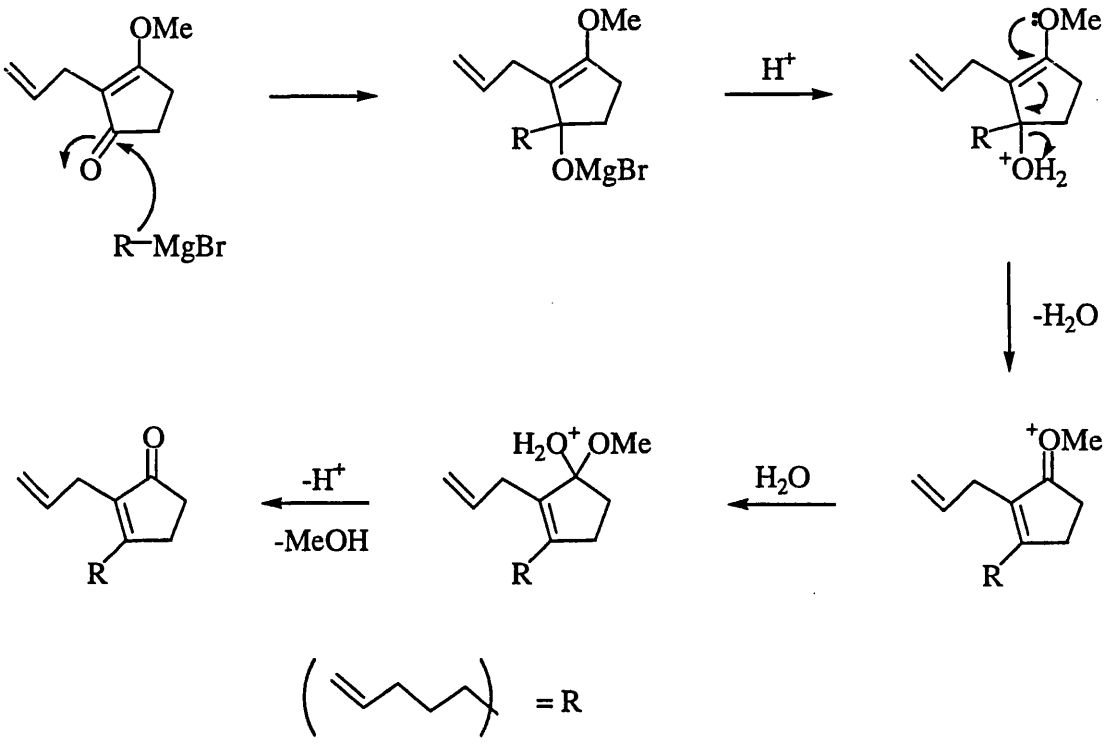
Scheme 2.5: Synthesis of triene **2.4**

a) i: 5-bromopentene, Mg turnings, Et_2O, 0 °C, 8 h, ii: 2 N HCl, rt, 30 min, 62 % over 2 steps.

Initial investigative reactions showed that low yields of the product formed when the Grignard reagent was added to enol ether **2.5**. This was also the case when more than a stoichiometric amount of enol ether **2.5** was used or when the reaction was performed at –78 °C. Best results were obtained when a solution of the enol ether **2.5** in diethyl ether was added to a solution containing two equivalents of the pentenylmagnesium bromide at 0 °C [6]. The mixture was warmed to room

temperature and stirred overnight before quenching with acid. Following this procedure yields of up to 62 % of the desired triene intermediate **2.4** were obtained.

A possible mechanism for the reaction is detailed in **Scheme 2.6** [3]:



Scheme 2.6: Proposed mechanism for the formation of triene **2.4**.

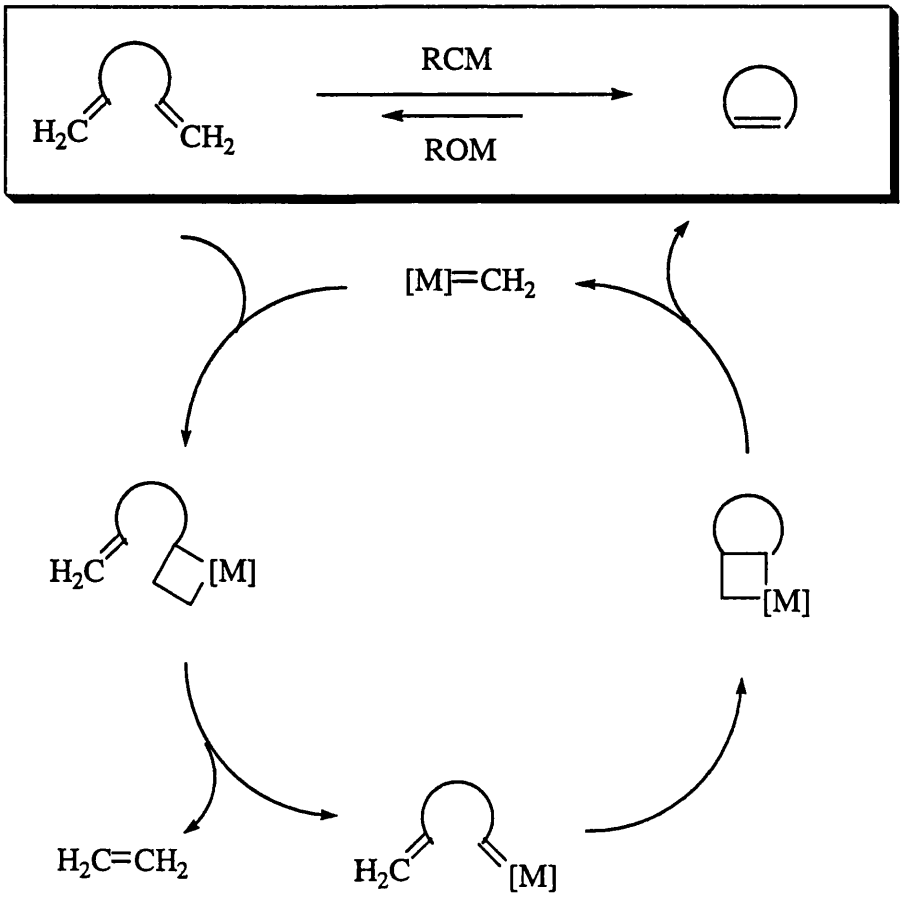
According to our synthetic plan, triene **2.4** is the ring closing metathesis (RCM) precursor to the [5-8] bicyclic system **2.3**.

2.32 *Ring-closing metathesis of triene 2.4*

Ring-closing metathesis (RCM) has emerged as a powerful synthetic tool and numerous reviews account for its wide applicability in the total synthesis of natural products[7 8 9 10 11]. This method of ring formation offers an alternative to the

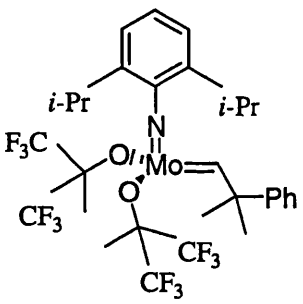
intramolecular ene reactions employed by Takeshita *et al* in their former total synthesis of cycloaraneosene [12].

The generally accepted mechanism for the RCM reaction consists of [2+2] cycloadditions and is known as the 'Chauvin' mechanism [11]. All individual steps of the catalytic cycle are reversible and ring-opening metathesis (ROM) competes with RCM (**Scheme 2.7**). However the equilibrium can be shifted in favour of the forward process: RCM is entropically driven because it generates two products from a single substrate. The volatility of one of the products, ethene (C_2H_4), shifts the equilibrium towards the desired cycloalkene.

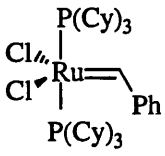


Scheme 2.7: The 'Chauvin' mechanism

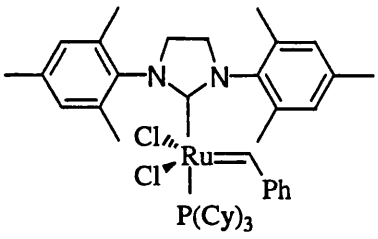
A range of (pre-)catalyts has been developed. Among them, the three most popular molybdenum and ruthenium catalysts are illustrated **Figure 2.1**:



2.13



2.14



2.15

Figure 2.1: Widely used RCM catalysts.

Schrock's tetracoordinated alkylidene species **2.13** constitute, the oldest established RCM catalyst of the three [13]. It must be handled in rigorously dried solvents and kept away from oxygen, which often renders its utilisation difficult. However, the high reactivity of the molybdenum complex **2.13** compensates for this inconvenience: catalyst **2.13** often reacts where other RCM catalysts fail to react and notably allows the formation of products containing a tri- or even tetra-substituted double bonds:

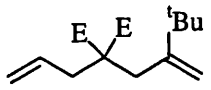
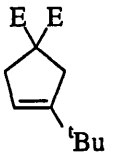
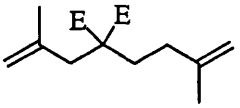
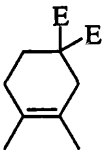
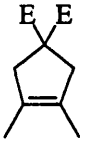
Entry	Substrates	Products	Time (h)	yield (%) using: 2.13	2.14	2.15
1			1	37	N.P.	100
2			1.5	52	N.P.	90
3			24	93	N.P.	31

Table 2.1 [14]: Relative reactivity towards hindered dienes of catalysts **2.13**, **2.14** and **2.15**

E = CO_2Et, N.P. = no product observed by ^1H NMR

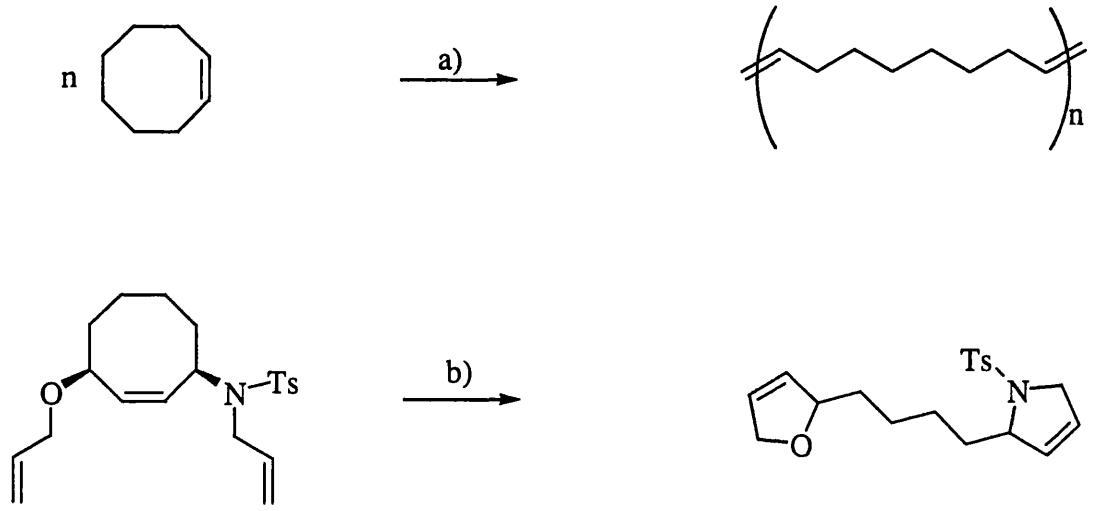
Unfortunately, catalyst **2.13** fails to tolerate a lot of common functionalities. In particular, the 'hard' $Mo^{(IV)}$ centre shows strong affinity for unprotected alcohol and carbonyls, inhibiting the catalytic activity of complex **2.13** [15].

On the other hand, Ru based catalysts **2.14** and **2.15** are more tolerant towards most oxygenated functionalities and a lot of functionalities in general (with the exception of sulfides [16]). These catalysts are also easier to handle owing to the fact that they are not moisture sensitive: a derivative of Ru complex **2.14** was shown to perform RCM in an aqueous medium [17]. However, the commercially available Grubbs' catalyst **2.14** generally shows lower activity than Schrock's catalyst **2.13** and notably fails to react with hindered dienes (**Table 2.1**, entries 1, 2 and 3). However, the modified Ru catalyst **2.15** has been recently shown to combine high reactivity with stability and tolerance towards various functionalities [18]. Its reactivity towards

hindered dienes is in many cases, at least comparable to Schrock's catalyst **2.13** (Table **2.1** entries 1 and 2). Although its applicability has not been fully explored yet, several groups have reported its synthesis [18] [19].

To date, RCM has provided access to various ring systems and, apart from very strained rings or small rings (cyclopropane, cyclobutane), all ring sizes have been eventually accessed [7] [11] [10]. Regardless of the steric hindrance on the diene moiety, the difficulty in ring-closing a given substrate is highly dependant on the size of the ring target.

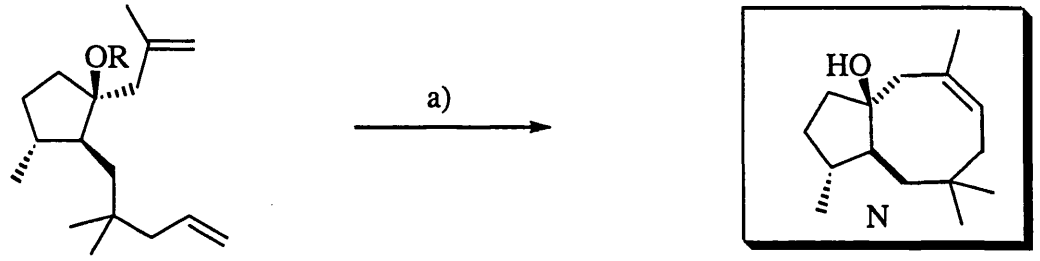
Due to their relatively high strain energy combined with the unfavourable entropic influence (probability of the chains meeting), RCM of medium rings (C_8 to C_{11}) has often been problematic [10]. A particular challenge has been the synthesis of 8-membered rings: cyclooctene is an excellent substrate for ring-opening metathesis polymerisation (ROMP) as shown in the well established Hüls-Vestnamer polymerisation process (**Scheme 2.8**). This particular property has also been exploited in ROM/RCM (ring-opening metathesis/ring-closing metathesis) strategy [9].



Scheme 2.8: Hüls-Vestnamer polymerisation process and ROM/RCM strategy.

a) Hüls-Vestnamer ROMP process; b) ROM/RCM: 10 mol % of **2.14**

Until 1998, only two groups claimed the synthesis of an 8-membered ring by metathesis, relegating the corresponding diene precursor to the rank of the worst substrates [7]. Recently however, a better understanding of the factors affecting the ring-closure gave access to natural products containing eight-membered ring *via* a RCM strategy [15 20 21]. It is now acknowledged that a successful synthesis of these medium-size rings requires the adequate conformation of the diene precursor.



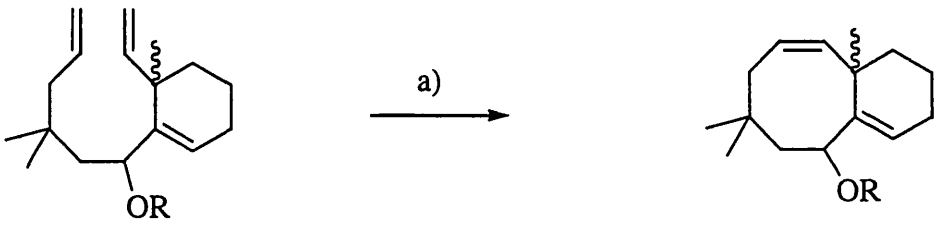
R = TMS

Dactylol

Scheme 2.9: RCM strategies towards the synthesis of dactylol.

a) i: 3 mol % **2.13**, hexane, 55 °C, 3 h, ii) TBAF, THF, 50 °C, 3 h, 92 % over 2 steps.

In the case of dactylol, the Thorpe-Ingold effect [22] induced by the *gem*-methyl substituents provided enough conformational bias to allow the construction of the eight-membered ring in very good yields.

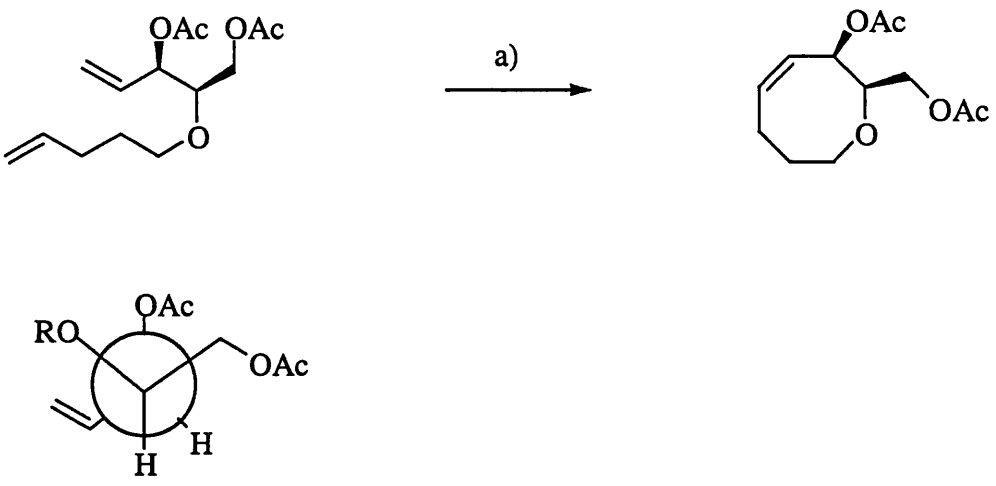


R = TES

Scheme 2.10: Prunet *et al* synthetic approach towards Taxol®.

a) i:10 mol % of **2.13**, benzene, 80 °C, 3 days, ii: TBAF.3H_2O, THF, 85 % over 2 steps.

In their study towards the total synthesis of Taxol®, Prunet *et al* [21] took advantage of the same effect and noted that the protection of the alcohol functionality with a bulky TES protecting group also contributed to provide the required conformational constraint and good yields of ring-closed material (**Scheme 2.10**).



Scheme 2.11: Crimmin's RCM approach towards (+)-laurencin

a) 7 mol % of **2.14**, CH_2Cl_2, 40 °C, 2 h, 73 %.

Crimmins and co-workers took advantage of the 'gauche effect' created by the vicinal stereocentres to enhance the ring-closing reaction by positioning the terminal dienes in a suitable conformation [20].

Although the Thorpe-Ingold effect and the 'gauche effect' provide a satisfactory explanation in many cases, they do not account for the earlier findings by Grubbs' and co-workers [23]:

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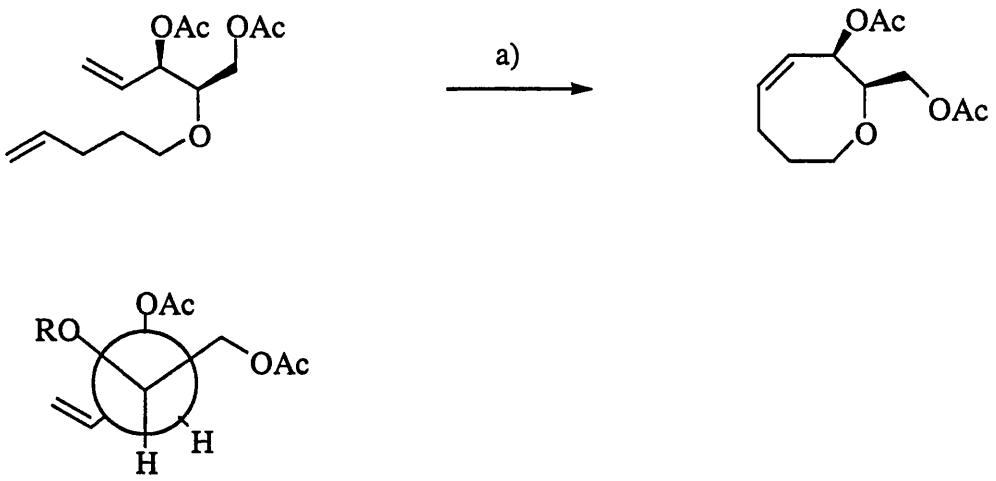

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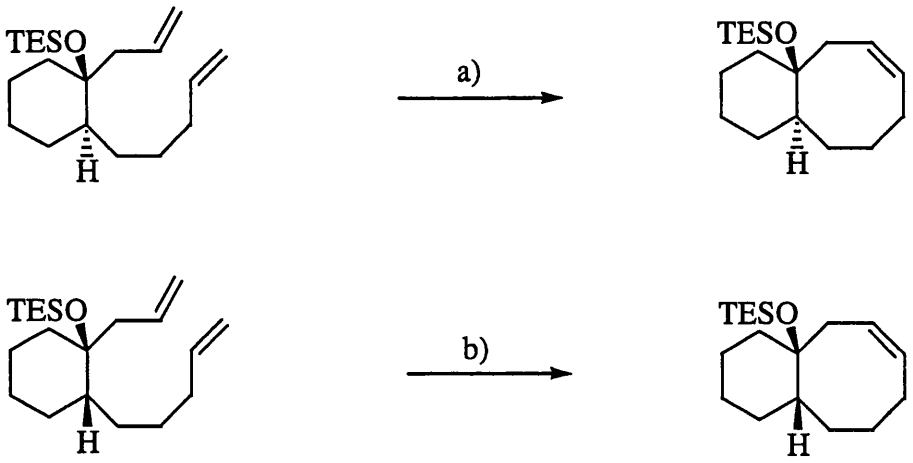


Scheme 2.12: Early eight-membered ring synthesis *via* RCM

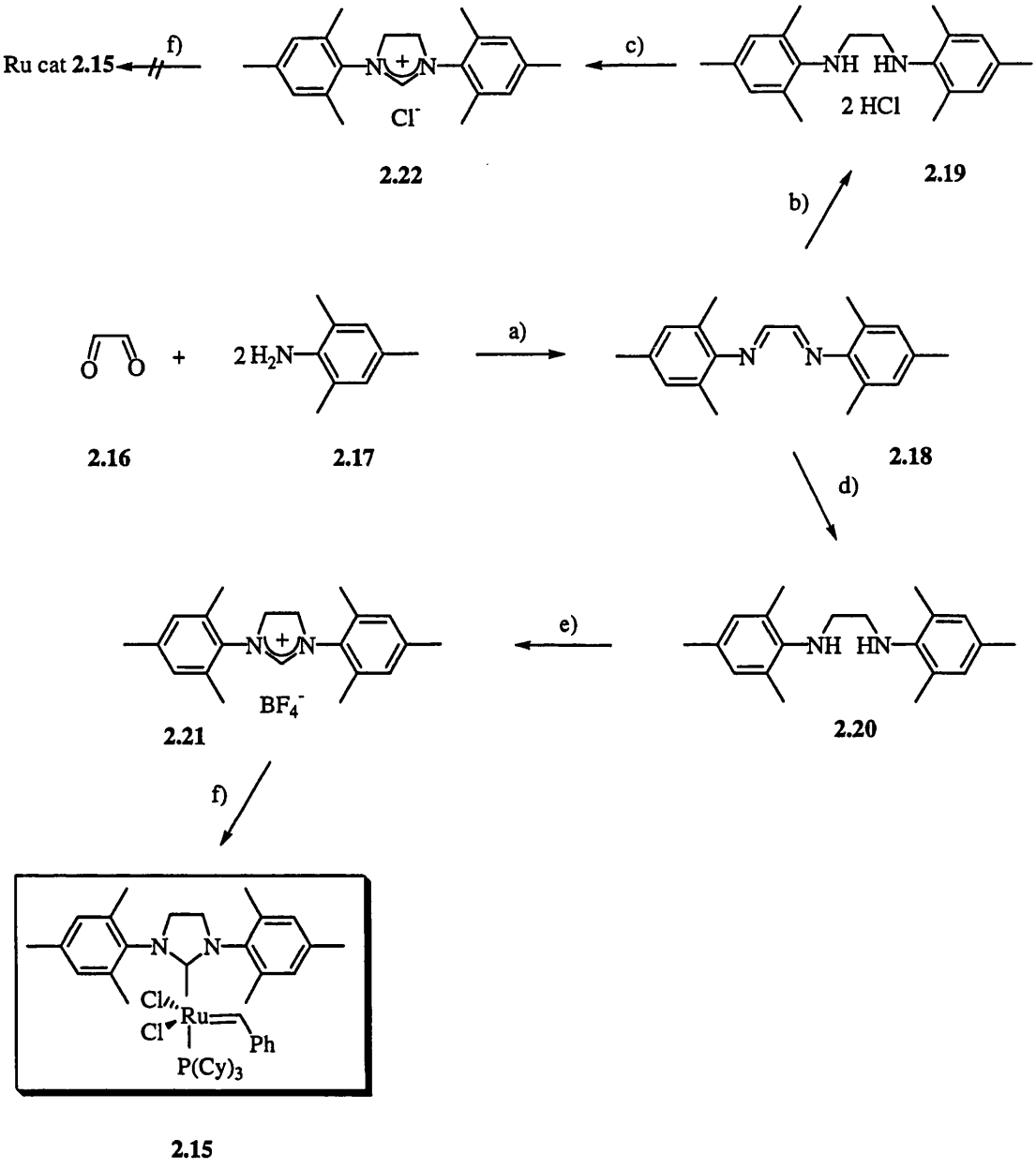
a) 5 mol % of **2.14**, benzene, 4 h, 25 °C, 75 %; b) 5 mol % of **2.14**, benzene, 25 °C, 20 h, 33 %.

This earlier report seemed to show that the *trans*-geometry pre-disposed to RCM while a *cis*-conformation was not favourable.

Finally, the potential of catalyst **2.15** has been seldom exploited in the area of medium ring metathesis and little is known about its potential.

Triene **2.4** exhibits a free carbonyl functionality, which guided our choice towards Ru catalysts **2.14** and **2.15** rather than Mo catalyst **2.13**. RCM with this last catalyst was however attempted in degassed dichloromethane at reflux (10 mol %, [triene] = 0.01 M), under glove box conditions. After 12 hours, no bicyclic product **2.3** was detected; the starting triene **2.4** was almost entirely recovered and the catalyst decomposed very rapidly (the reaction mixture turned dark brown within the first 5 min, against the typically reported yellow colour [13]). The practical difficulties encountered combined with the inappropriate nature of the substrate led us to abandon RCM efforts with Schrock's catalyst.

We then sought to investigate the RCM of triene **2.4** using Ru catalyst **2.14** and **2.15**. At first, catalyst **2.15** was synthesised according to a combination of previously reported procedures [18 19 24]:



Scheme 2.13: Synthesis of Ru catalyst **2.15**.

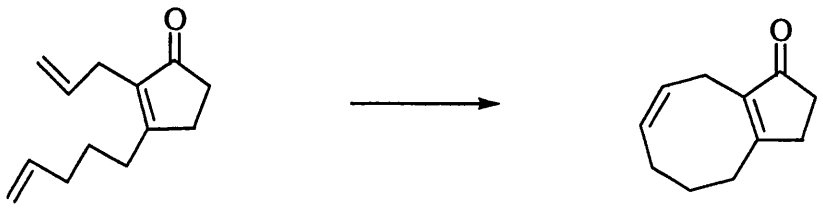
a) 2:1 IPA:H_2O, 16 h 23 °C, 4 h 60 °C 55 %; b) i: $NaBH_4$, MeOH, 0 °C, ii: conc. HCl, 85 % c) $HC(OEt)_3$, 120 °C, 86 % d) i: $NaBH_4$, MeOH, 0 °C, ii: conc. HCl, iii: Na_2CO_3 until pH = 8, 72 % e) $HC(OEt)_3$, $NaBF_4$, 120 °C, 82 %; f) i: *t*-BuOK, THF, ii: Ru cat **2.14**, toluene, 80 °C, 43 %.

Condensation of glyoxal **2.16** with two equivalents of 2,4,6-trimethylaniline **2.17** and subsequent reduction of the resulting *bis*-imine **2.18** led, after precipitation with HCl, to the dihydrochloric salt **2.19** in 47 % overall yield [24]. Alternatively, free amine

2.20 can also be obtained from the same precursors, if the dihydrochloric salt is neutralised with Na_2CO_3 or KOH [19]. Two adjacent synthetic routes were then pursued, leading to the formation of the carbenoïd precursors **2.21** and **2.22**, upon condensation with triethylorthoformate (in the presence of $NaBF_4$ in the case of **2.21**). For both salts, the analytical data was found to match with the literature [19 24]. The last step consisted of a ligand exchange reaction where Ru complex **2.14** was reacted with the carbene species generated from **2.21** or **2.22**. Interestingly, ligand exchange did not take place when the chlorine salt **2.22** was used, but proceeded as reported [19] when the tetrafluoroborate salt **2.21** was employed. This result revealed the importance of the counter anion: the larger and more charge-diffused ('softer') BF_4^- is preferable to the smaller and 'harder' Cl^-.

Ru complex **2.15** was obtained as a red microcrystalline solid in 43 % yield (for the last step) and the analytical data was found to be consistent with the literature [19].

With both Ru catalyst **2.14** and **2.15** in hand, we decided to re-investigate the ring closing metathesis of triene **2.4**:



2.4 **2.3**

Scheme 2.14: RCM of triene **2.4**.

At first, reactions with commercially available Grubbs catalyst were examined:

entry	solvent[a]	temperature (°C)	ratio P:SM	yield %
1	DCM	20	2.9:1	15
2	DCM	40	8.0:1	32
3	Benzene	60	3.4:1	21[b]

Table 2.3: RCM with Ru cat **2.14**

a: All solvents were degassed. b: yield determined by ^{1}H NMR. For all reactions: [substrate **2.4**] = 0.01 M, reaction time of 36 h, 10 mol % catalyst loading. ratio P:SM = ratio bicycle **2.3**:triene **2.4**.

Previous explorative studies on the same substrate with catalyst **2.14** revealed that RCM was best achieved with 10 mol % of catalyst and 0.01 M of triene **2.4** [6]. Furthermore, practical complications rendered the isolation of the bicyclic product **2.3** difficult: both enones **2.3** and **2.4** co-eluted on SiO_2 and could only be separated after two successive flash columns chromatography: a conventional system (SiO_2, light petroleum-diethyl ether, 80:20) followed by flash chromatography on doped SiO_2 ($SiO_2/AgNO_3$, diethyl ether).

Unfortunately, the ring-closing metathesis of triene **2.4** could never be driven to completion employing catalyst **2.14**. The best results were obtained DCM at reflux where both the isolated yield and the P:SM ratio were the highest (entry 2, 8:1 ratio, 32 % isolated yield). Milder conditions (entry 1) or higher temperatures in benzene (entry 3) resulted in lower P:SM ratio and lower yields. It is believed that over prolonged reaction times (36 h) at temperature higher than 40 °C the catalyst decomposed. Furthermore, the volatility of enone **2.3** and **2.4** ruled out the use of higher boiling solvents (for example toluene) [6].

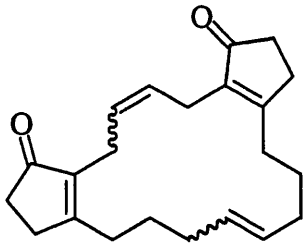
We then examined the RCM of triene **2.3** employing Ru catalyst **2.15**:

entry	**2.15** (% mol)	solvent[a]	temperature °C	ratio P:SM	ratio P:Byp	yield %[b]
1	10	DCM	20	2.45:1	Byp n. f	21
2	10	DCM	40	R.C	2.4:1	49
3	10	Benzene	60	R.C	4.4:1	57
4	5	Benzene	60	R.C	7.4:1	71
5	1	Benzene	60	0.36:1	Byp n. f	> 5

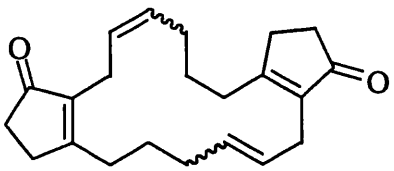
Table 2.4: RCM of triene **2.4** with Ru catalyst **2.15**

a: all solvents were degassed. b: all yields were determined by ^{1}H NMR. For all reactions: [substrate **2.4**] = 0.01 M, reaction time of 36 h. R.C = reaction complete. Byp n. f = by-products **2.23, 2.24** were not formed. Ratio P:SM = Ratio bicycle **2.3**:triene **2.4**. ratio P:Byp = ratio bicyle **2.3**: by-products **2.23, 2.24**.

At first, the experimental conditions employed with Ru catalyst **2.15** were reproduced ([triene **2.4**] = 0.01 M, catalyst loading of 10 mol %). Under mild conditions (entry 1, 20 °C in DCM) the reaction was not driven to completion (after 36 hours) and poor yields of bicyclic enone **2.3** were achieved. However, at higher temperatures (entries 2 and 3) the ring-closing metathesis of triene **2.4** reached completion within 36 hours. Concomitantly, the formation of a by-product, dimer **2.23** and/or **2.24** was observed:



2.23



2.24

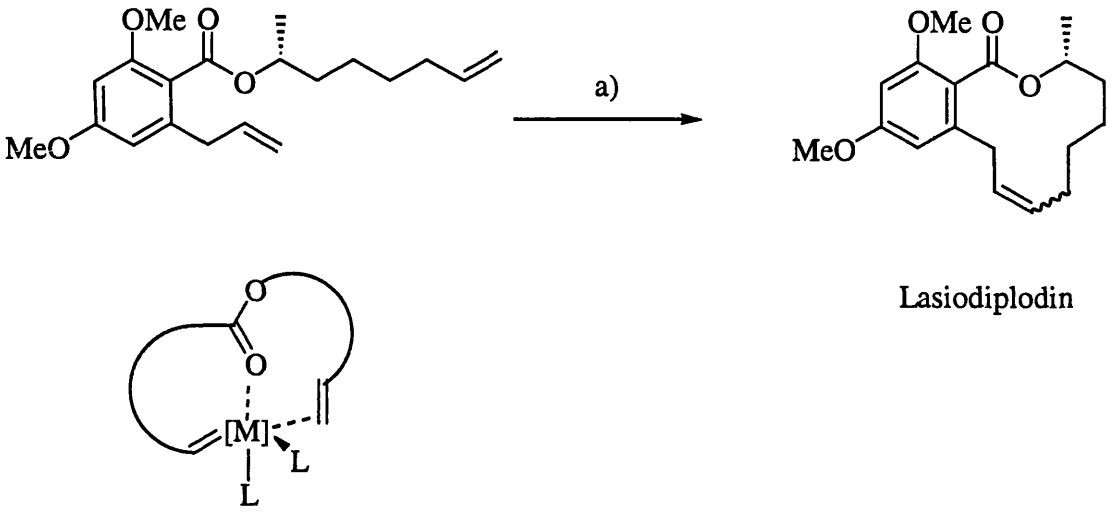
Figure 2.2:Proposed structures of dimers **2.23** and **2.24**.

^{1}H NMR analysis revealed the presence of four alkene protons (2H, apparent triplet, 6.17 ppm 1H, multiplet 5.9-6.1 ppm, 1H multiplet 5.77-5.84 ppm) accounting for the presence of the double bonds of the macrocycle of **2.23** or **2.24**. ^{13}C NMR inspection showed the presence of 21 distinct signals (notably two quaternary carbons corresponding to two carbonyls, 208.28 ppm, 209.15 ppm) and led us to believe that both dimers **2.23** and **2.24** were formed. The molecular ion (FAB^{+}, 7 %, 325.1) detected by mass spectrometry justified the formation of the proposed dimeric structures.

Higher temperature (entry 3, 60 °C in benzene) improved the formation of bicycle **2.3** (ratio P:Byp = 4.4:1) and the yield of the reaction (57 %). More importantly, for a lower catalyst loading (entry 4, 5 mol %) under the same conditions (benzene, 60 °C), the formation of dimers **2.23** and **2.24** was minimal (ratio P:Byp 7.4:1) and bicyclic enone **2.3** was formed in good yields (71 %). However, at even lower catalyst loading (entry 5, 1 mol %) dramatic decrease in the formation of product **2.3** was observed and, as with Ru catalyst **2.14**, the reaction did not reach completion.

Finally, investigations were directed towards the role played by the enone moiety during the RCM process. Fürstner and co-workers established that the presence of a

moderate Lewis basic functionality (ester, amide) could act as a 'relay' functionality and influence the outcome of the reaction [25]:



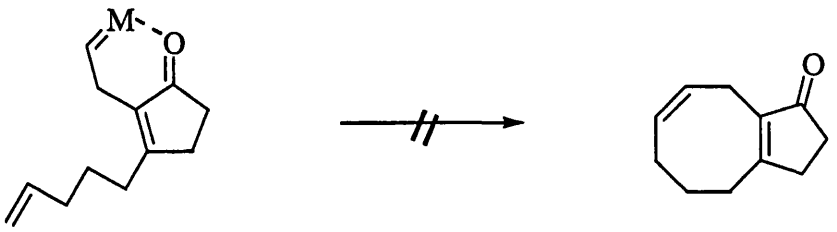
Lasiodiplodin

2.25

Scheme 2.15: Application of the 'relay' theory in the synthesis of Lasiodiplodin

a) 6 mol % of **2.14**, DCM, reflux, 94 %, E:Z = 2.3:1

If this moderately Lewis basic functionality (ester, amide) is correctly positioned and if chelate structure **2.25** is not too stable, the cyclisation is favoured over oligomerisation pathways. Although little is known on the role of an enone functionality, one can imagine that Ru catalyst **2.14** and/or **2.15** could chelate with the carbonyl and the closer terminal alkene moiety:



2.26 **2.3**

Scheme 2.16: Proposed chelate structure

M = RCM catalyst **2.14** or **2.15**.

The resulting six-membered chelate **2.26** could be stable enough to prevent catalyst **2.14** or **2.15** from reacting further. However, this outcome can be rectified upon the addition of a weak Lewis acid Ti(O*i*Pr)$_4$ and, in the case of a chelating ester functionality, smooth RCM usually follows [26]. Our last studies sought to investigate the RCM of triene **2.4** employing a binary system comprising catalytic amounts of Ru catalyts **2.14** or **2.15** and a substoichiometric amount of Ti(O*i*Pr)$_4$:

entry	Ru catalyst	solvent[a]	temperature °C	ratio P:SM	ratio P:Byp	yield %[b]
1	**2.14**	DCM	40	2.9:1	Byp n.f.	24
2	**2.15**	DCM	40	R.C	1.5:1	33

Table 2.5: RCM of triene **2.4** with Ti(O*i*Pr)$_4$ and Ru cat **2.14** or **2.15**.

a: DCM was degassed. b: all yields were determined by ^{1}H NMR For all reactions: [substrate **2.4**] = 0.01 M, reaction time of 36 h, 0.3 eq. of Ti(O*i*Pr)$_4$ were used. R.C = reaction complete. Byp n. f = by-products **2.23** or **2.24** not formed. Ratio P:SM = Ratio bicycle **2.3**:triene **2.4**. ratio P:Byp = ratio bicyle **2.3**: by-products **2.23** or **2.24**.

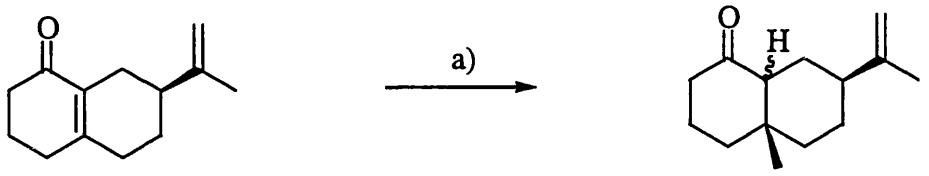
Experimental conditions comparable to our previous studies (**Table 2.4** and **2.3**) were reproduced ([triene] = 0.01 M, catalyst loading of 10 mol %). To our surprise, the addition of $Ti(OiPr)_4$ contributed to reduce the efficiency of Ru catalysts **2.14** and **2.15**. By comparison with our previous studies (**Table 2.3** entry 2 and **Table 2.4** entry 2) the ratio P:SM and/or the ratio P:Byp were lower (2.9:1, 1.5:1 against 8.0:1 and 2.4:1 respectively) and bicycle enone **2.3** was formed in lower yields (22 % and 33 % against 32 % and 49 % respectively). The coordination of Ru catalyst **2.14** or **2.15** to the carbonyl of triene **2.4** might therefore have had a beneficial effect on the yield of the RCM reaction. As a result, the reaction might be preferably initiated at the closest terminal alkene to the carbonyl of triene **2.4**. However, further studies (for example with triene **2.4** bearing a protected carbonyl) are required in order to verify these latest findings.

2.33 *1,4-Addition at the ring-junction B-C*

With bicyclic enone **2.3** in hand, we envisaged the introduction of the methyl group at the ring-junction B-C *via* a conjugate addition.

Organocuprate reagents provide a powerful method for C-C bond formation. Their 'soft' nucleophilicity is particularly well suited for the specific 1,4-addition to α,β-unsaturated carbonyls (enones, enals and enoates) and their chemistry has been thoroughly reviewed [27] [28]. However, hindered substrates such as β,β-disubstituted enones are often a problematic case: low yields are usually observed with Gilman cuprates (R_2CuLi or R_DR_TCuLi where R_T = transferable group, R_D = residual ligand). Fortunately, in 1977, Yamamoto *et al* discovered a new organocuprate reagent, $RCu.BF_3$ [29]. This reagent, which is stable at low temperature (-78 °C) combines the nucleophilicity of a Gilman cuprate (attack at the β-position) with the electrophilicity

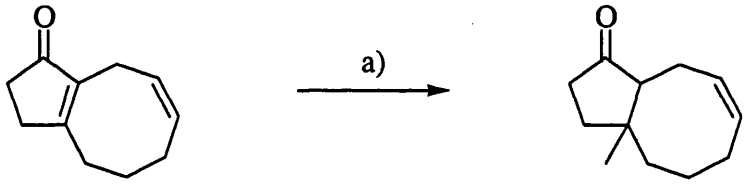
of the Lewis acid $BF_3.Et_2O$ (activates the carbonyl). As a result, enhanced reactivity is observed and Yamamoto's cuprate has provided the solution to many synthetic problems, where Gilman cuprates failed to react [29]:



Scheme 2.17: 1,4-Addition on a bicyclic enone using $MeCu.BF_3$

a) CuI, MeLi, $BF_3.Et_2O$, Et_2O, -78 °C, 47 %.

Buphaty and co-workers noted that Me_2CuLi completely failed to react while $MeCu.BF_3$ promoted 1,4-addition with bicyclic enone **2.27** in reasonable yields [29]. In turns, we considered the 1,4-addition of $MeCu.BF_3$ to bicyclic enone **2.3**:



2.3 **2.2**

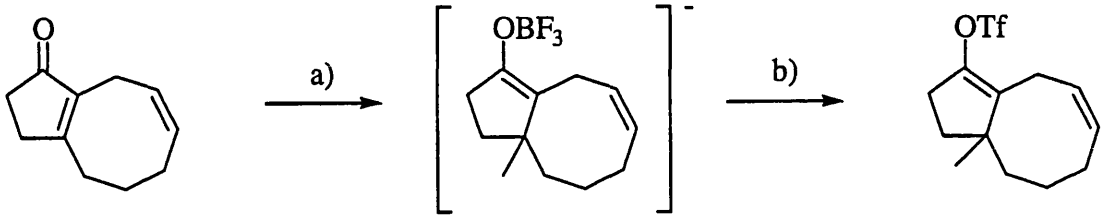
Scheme 2.18: 1,4-Addition with $MeCu.BF_3$

a) MeLi, CuI, $BF_3.Et_2O$, Et_2O, -78 °C, 53 %,30 % de.

Reasonable and reproducible yields were achieved (53 %) and the introduction of the new methyl group resulted in the appearance of two new resonance signals in ^1H NMR (s, 0.91 ppm and 1.14 ppm). The diastereoisomeric excess was also taken into

account and concomitant analysis by ^{1}H NMR spectroscopy and chiral GC revealed a moderate de (42 % by ^{1}H NMR and 30 % by chiral GC).

Furthermore, we attempted to trap the resulting enolate *in situ* with triflic anhydride:



2.27 **2.28**

Scheme 2.19: Attempt to trap boron-enolate **2.27** *in situ*

a) MeLi, CuI, $BF_3.Et_2O$, Et_2O -78 °C, %; b) Et_3N or MeLi, Tf_2O, -78 °C.

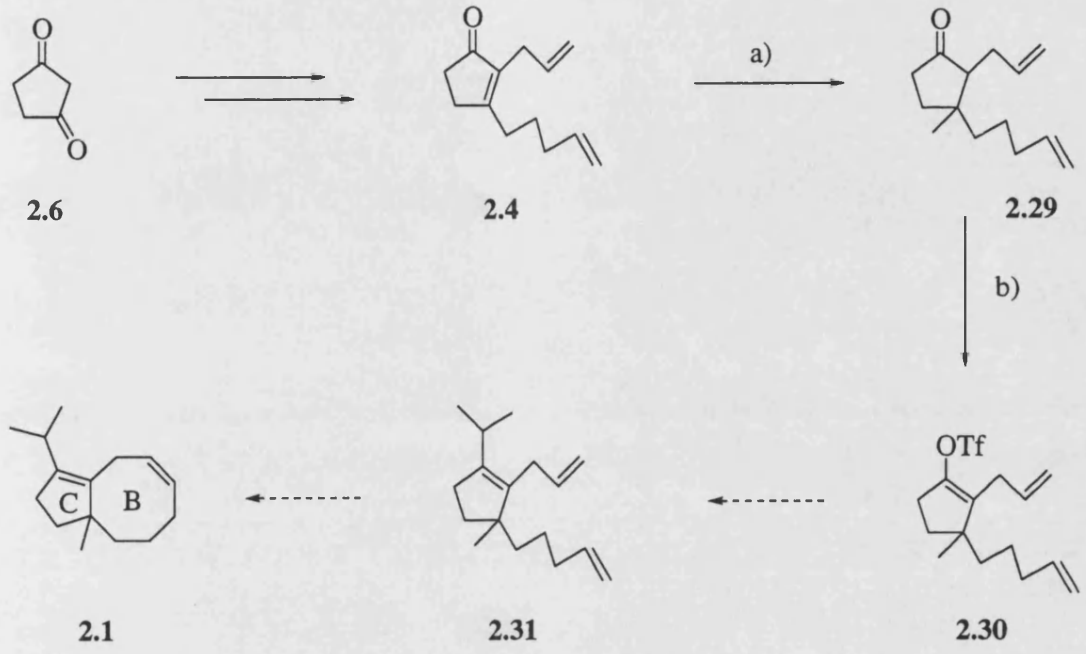
Unfortunately, the O-alkylated **2.28** product was never isolated, even when transmetallation was attempted with triethylamine or methyllithium *prior* to the addition of triflic anhydride. The boron-enolate **2.27** proved to be unreactive and the methylated bicycle **2.2** was persistently recovered.

Furthermore, it was found difficult to synthesise the methylated bicyclic enone **2.2** on a sufficient scale because the cumbersome isolation of enone **2.3** drastically limited the efficiency of our strategy.

2.4 Alternative synthetic route towards ring B-C.

An alternative route was promptly designed. This time, our aim was to perform RCM with Schrock's catalyst on an adequate substrate free of any oxygen functionalities. Furthermore, the coupling of the isopropyl side-chain was still to be investigated.

The new synthetic route detailed below provided rapid access to triflate **2.30** and investigative studies in this area could then be envisaged:



Scheme 2.20: Alternative route towards ring system B-C.

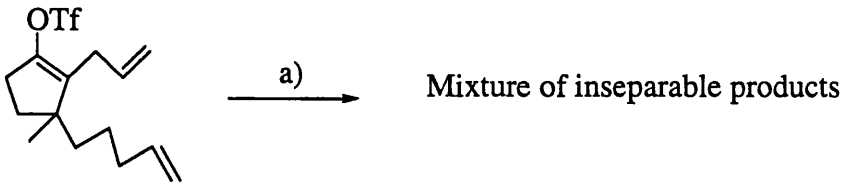
a) $MeCu.BF_3$, Et_2O, -78 °C, 50 % b) i: KHMDS, THF, rt, 12 h, ii 2-[*N,N*-Bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, 60 %.

Triene **2.4** was synthesised in three steps *via* the same synthetic route detailed before. This time however, the 1,4-addition was performed on the monocyclic triene **2.4**. Yamamoto's cuprate was again the reagent of choice and yields were comparable to those obtained with bicyclic enone **2.3** were achieved (50 %). The diastereoisomers were formed in differing amounts giving rise to 31 % de (0.83 ppm and 0.92 ppm, by ^1H NMR).

The thermodynamic enolate of ketone **2.29** was then generated with KHMDS in THF. After 12 hours at room temperature the enolate was reacted with 2-[*N,N*-*Bis*(trifluoromethylsulfonyl)amino]-5-chloropyridine to provide vinyl triflate **2.30**.

^{13}C NMR analysis accounted for the absence of a carbonyl, and the protons of the methyl group give rise to a unique singlet at 1.07 ppm in the ^{1}H NMR spectrum.

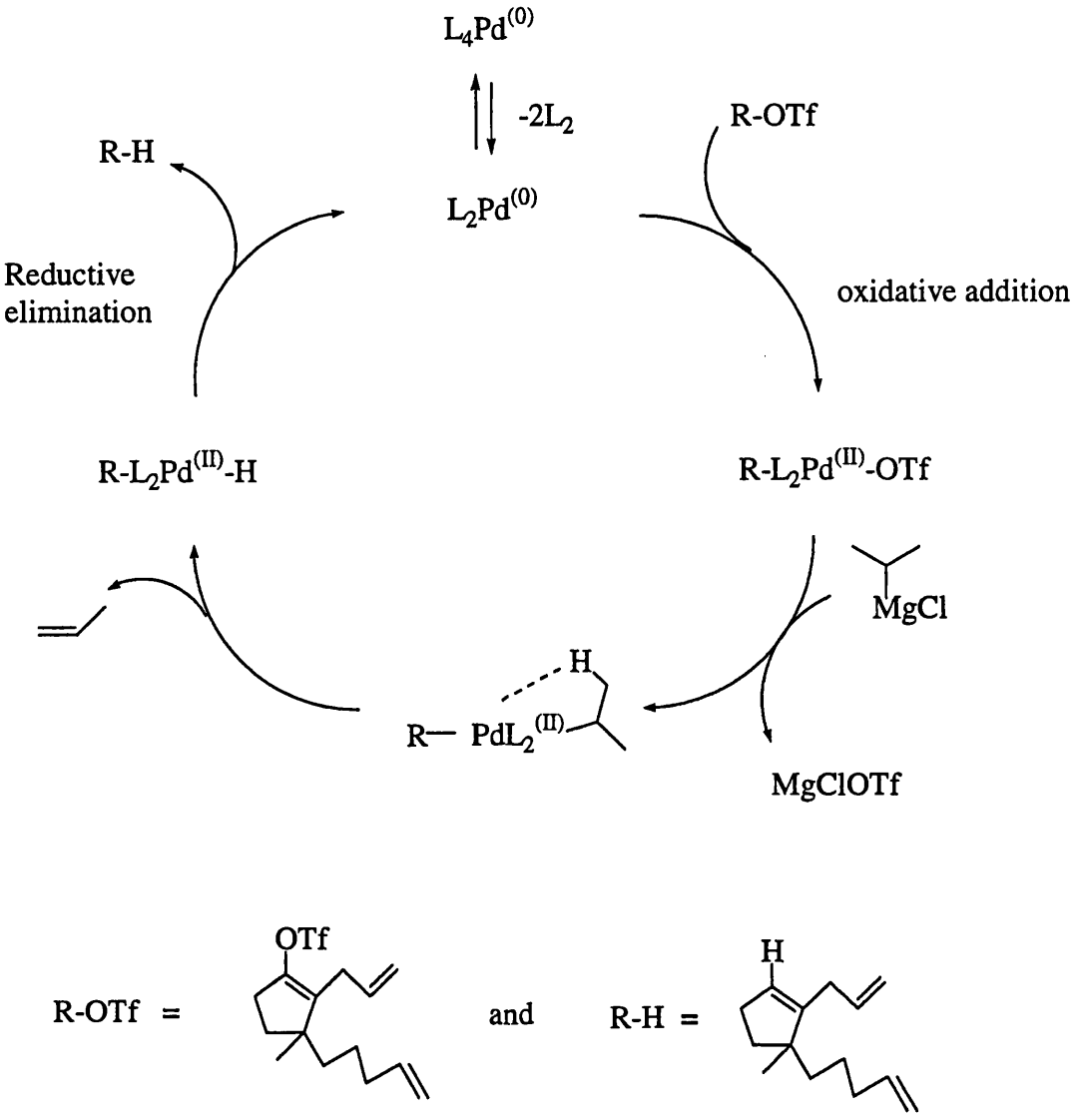
We then attempted to couple the isopropyl side-chain with vinyl triflate **2.30**. It was previously found that on a very similar system McMurry type coupling with organocuprate reagents failed [6]. However, a palladium-catalysed cross-coupling reaction proved to be a successful alternative, at least with the simple Grignard reagent methylmagnesium bromide [6]. Our first attempt aimed to reproduce the same reaction conditions, with commercially available isopropylmagesium chloride:



Scheme 2.21: Palladium-catalysed cross-coupling with $Pd(PPh_3)_4$.

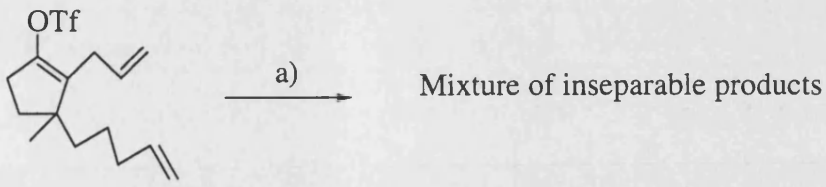
a) *i*-PrMgCl, 10 mol % of $Pd(PPh_3)_4$, THF, reflux.

Although the reaction proceeded to completion, a complex mixture of non-polar (R_f = 0.7 in petroleum ether) co-eluting products was obtained. We reasoned that β-hydride elimination promoted by the palladium catalyst might have taken place and competed with the expected coupling reaction. A proposed catalytic cycle for this competing transformation is outlined below:



Scheme 2.22. Competing β-hydride elimination.

In their studies towards the coupling of aryl halide with branched Grignard reagents, Hayashi and co-workers reported that β-hydride elimination was strongly dependant on the nature of the phosphine ligand and therefore on the P-Pd-P bond angle [30]. Notably, dppf (which gives rise to a large P-Pd-P bond angle of 99.07 °) allowed smooth cross-coupling of various aryl bromides with *s*-butylmagnesium bromide [30]. We hoped that the same conditions would also help to promote the cross-coupling reaction in our system:

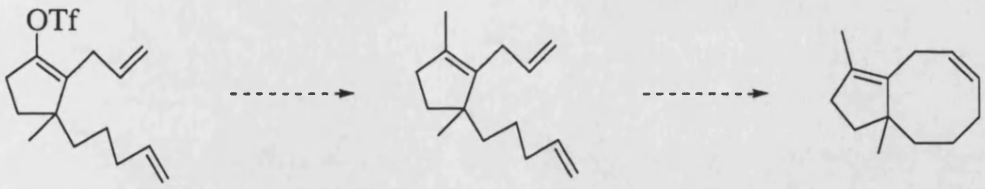


Scheme 2.23 Palladium-catalysed cross-coupling with dppf.

a) *i*-PrMgCl, 10 mol % of $dppfPdCl_2$, THF, reflux or rt.

Unfortunately, whether the reaction was performed at room temperature or in THF at reflux, the same mixture of inseparable products persisted (R_f = 0.7 in petroleum ether). The structure of any of these products remains unknown as their separation could never be successfully achieved.

As a result, the subsequent RCM reaction mediated by Schrock's catalyst could not be investigated. In the future, in order to evaluate the potential of Mo catalyst **2.13** on our system, the related and perhaps more accessible precursor **2.32** could be an interesting target:



2.30 **2.32** **2.33**

Scheme 2.24: Future development towards a Schrock's mediated RCM.

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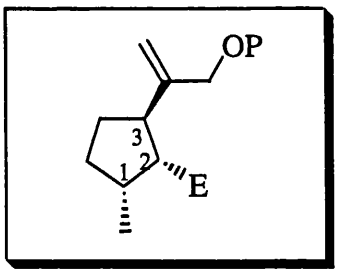
Chapter 3

Towards the Synthesis of Ring A

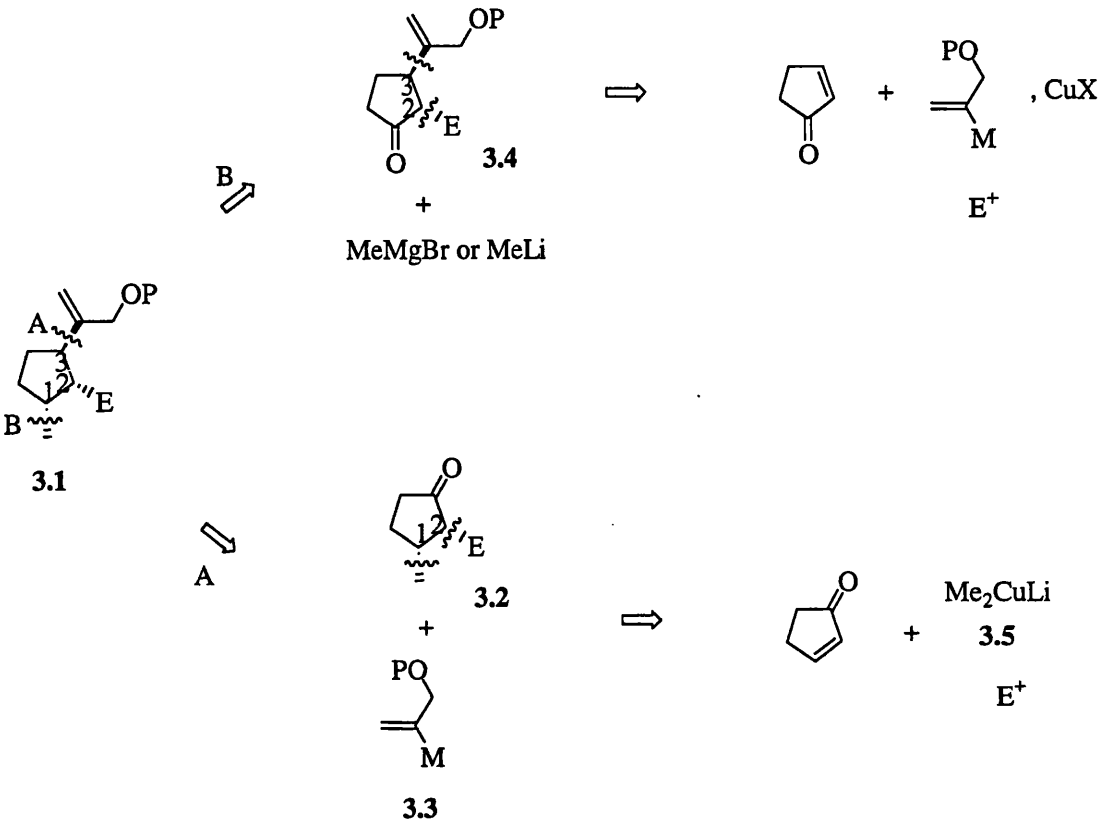


Where E = $-CO_2Me$, $-CH_2OH$ or $-CH_2Br$
P = protecting group

Figure 3.1: Ring A, general structure.

The left hand-side of cycloaraneosene, ring A, consists of a tri-substituted five-membered ring bearing a methyl group, a functionalised carbon E (ester, secondary alcohol or halogenated functionality) and an exocyclic *gem*-alkene side-chain. Three tertiary carbon stereocentres make up the stereochemistry of the molecule: the relative *trans*-geometry C_2-C_3 corresponds to the [5-8] *trans*-ring-junction A-B. The absolute configuration at C_1 is (*R*) and C_1 and C_2 bear a relative *cis*-geometry.

We embarked first on the racemic synthesis of ring A. However, the design of our synthetic strategy takes the stereochemistry issue into account. The general retrosynthetic analysis is outlined **Scheme 3.1**:



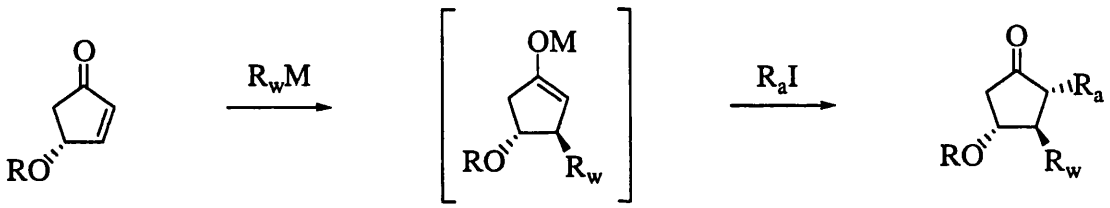
Scheme 3.1: Retrosynthetic analysis

We reasoned that the first disconnection could be either at carbon C_2 or carbon C_3: as a result two distinct but closely related synthetic routes A and B would be investigated. The first one, route A, commences with the disconnection of the exocyclic side chain at carbon C_3, and in the forward sense, ketone **3.2** would be the key intermediate from which the coupling of a metallated derivative of *gem*-alkene **3.3** would be envisaged. Further disconnection leads to commercially available cyclopentenone. A 1,4-addition with dimethylcuprate **3.5** followed by *in situ* trapping of the resulting enolate with the appropriate electrophile E constitutes the key step of our synthetic route.

Alternatively, the second route B proceeds *via* a similar 2,3-disubstituted cyclopentanone **3.4** intermediate but this time the exocyclic side-chain would be introduced first performing a copper mediated 1,4-addition followed, by *in situ* trapping of the resulting enolate with a suitable electrophile E.

In both cases, chirality could be introduced if the 1,4-addition is performed asymmetrically. Numerous methods reporting the use of chiral ligands are available from current literature [1-4] [5, 6].

Overall, this strategy was inspired by the method developed by Noyori and co-workers for the synthesis of prostaglandins [7]:



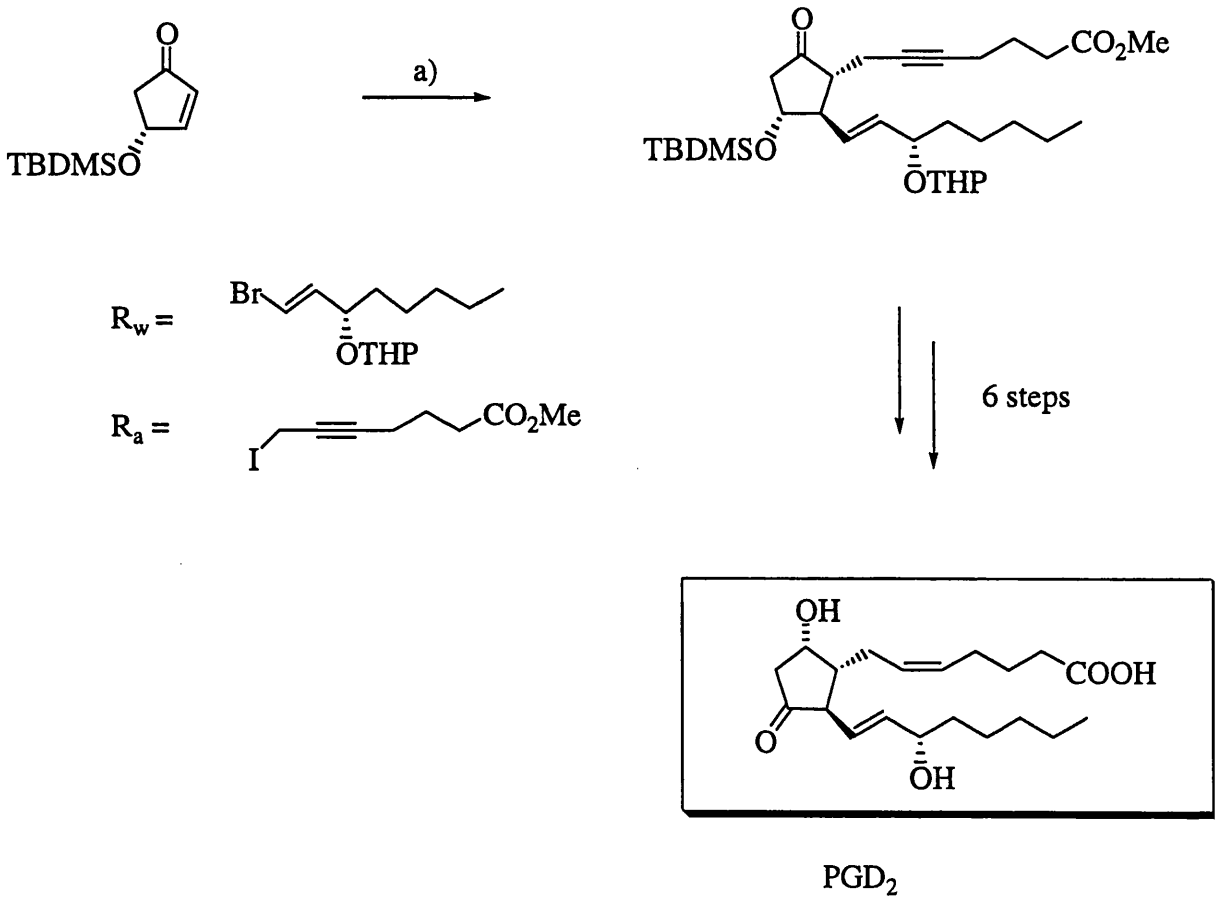
3.6 **3.7** **3.8**

R = bulky protecting group (in general TIPS or TBDMS).

Scheme 3.2: Noyori's general approach to prostaglandins [8]

Commercially available and enantiomerically pure cyclopentenone derivative **3.6** undergoes 1,4-addition with the organocuprate derivative $R_\omega M$. The resulting enolate **3.7** is then trapped *in situ* with a suitable electrophile $R_\alpha X$. In general, very reactive electrophiles such as allyl iodides and/or aldehydes are required. Furthermore, Noyori noted that the presence of stoichiometric amounts of *tri*-butylphosphine at the 1,4-addition stage in combination with transmetallation of the enolate with

chlorotriphenylstannane and the use of polar co-solvent (HMPA or DMPU), improved the C-alkylation step and yield of the overall process. The stereoselectivity of the 1,4-addition is directed by the bulky protected alcohol functionality at C_4 (R = TIPS in general). Subsequently, trapping of the resulting enolate takes place selectively *anti* with respect to the newly introduced R_ω group to produce ketone **3.8**. A typical example, arbitrarily chosen amongst numerous efficient syntheses of prostaglandin compounds by Noyori and co-workers, is depicted next page [7]:

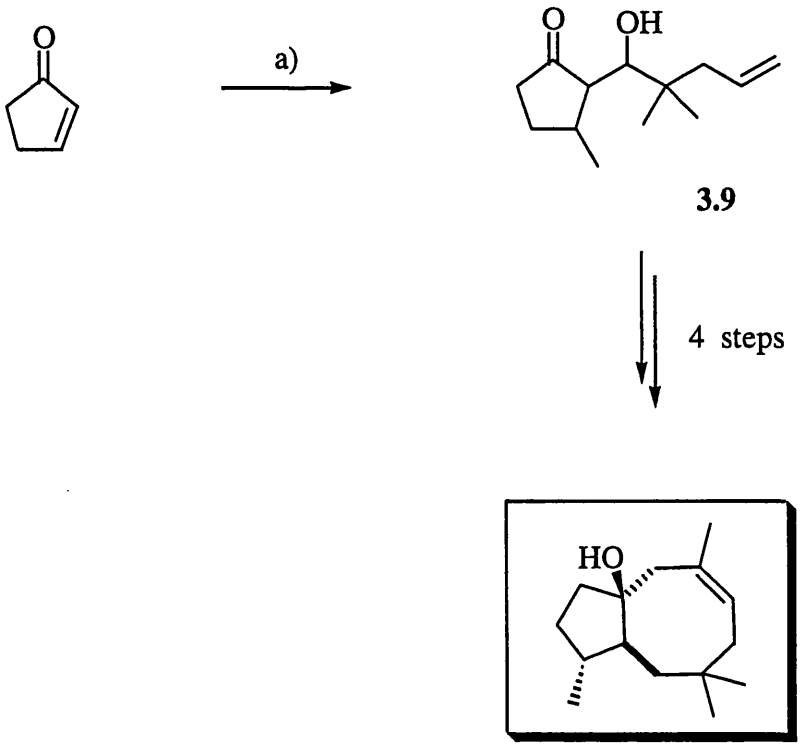


Scheme 3.3: Noyori's synthesis of PGD_2.

a) i: R_wLi, CuI, *n*-Bu_3P, ii: Ph_3SnCl, HMPA, iii: R_aI, 76 % overall yield.

No more than seven steps were required to access prostaglandin PGD_2. Furthermore, this versatile strategy has been applied to the total synthesis of several other members of the prostaglandin family [7].

This efficient method, which allows rapid entry to 2,3-disubstituted ketones has also inspired recent synthetic strategies. Feringa and co-workers [9] took advantage of it in a novel total synthesis of PGE_1. Fürstner *et al* also adapted this strategy to the synthesis of key 2,3-cyclopentanone **3.9** *en route* towards the total synthesis of dactylol (**Scheme 3.4**) [10]. It is notable that the rather cumbersome transmetallation with chlorophenylstannane and the use of polar additives (such as highly toxic HMPA) can be avoided in the case of 1,4-additions with simple organocuprate reagents such as dimethylcuprate:

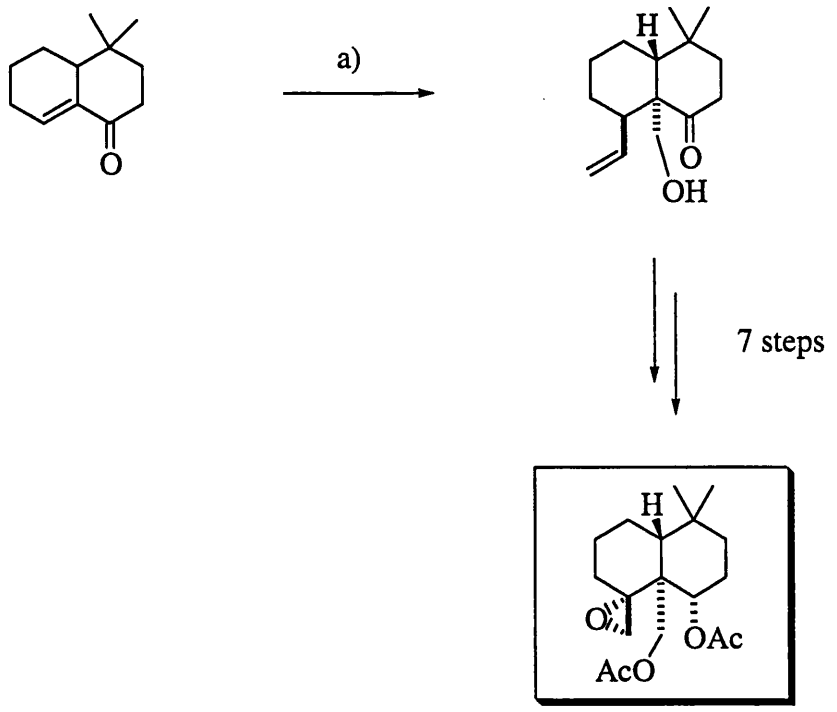


Dactylol

Scheme 3.4: Fürstner's synthesis of dactylol.

a) i: MeLi, CuI, *n*-Bu_3P, Et_2O, -78 °C to -40 °C, ii: 2,2-dimethyl-4-pentenal, -78 °C to rt, 77 % overall yield.

In our case, a single functionalised carbon has to be introduced at the α-position (relatively to the carbonyl). Only a few procedures are available from the literature, [11] and the use of monomeric formaldehyde is perhaps the most popular method. As a typical example, the total synthesis of a polyoxygenated *trans*-decalin [12]:



Polyoxygenated *trans*-decalin

Scheme 3.5: 1,4-Addition/enolate trapping with monomeric paraformaldehyde.

a) i: CuBr.Me_2S, H_2C=CHMgBr, THF, -50 °C, ii: monomeric H_2CO, THF, -50 °C; iii: NH_4Cl, 63 % overall yield.

Finally, the synthesis of the exocyclic side-chain **3.3** will have to be investigated separately and it is the object of the next section.

3.1. Synthesis of the side chain

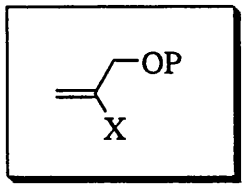


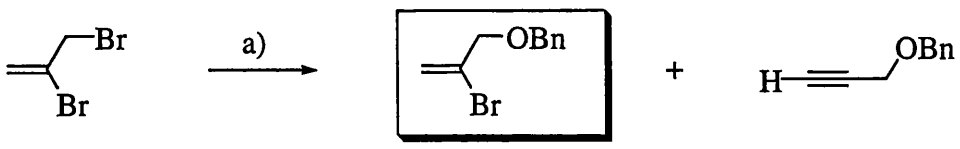
Figure 3.2: General structure of the side-chain

P = Protecting group, X = Br, $SnBu_3$.

According to our synthetic strategy, the adequate side-chain consists of a terminal *gem*-alkene bearing a protected oxygenated functionality and a masked vinyl anion. We reasoned that either a protected alcohol or a protected aldehyde could be introduced, while a bromide or a trialkylstannane group could occupy the *gem*-position (both of which would readily exchange for a Li atom to reveal the vinyl anion).

3.11. *Side-chain bearing a protected alcohol*

The protected alcohol **3.11** was obtained in one step from commercially available 2,3-dibromopropene **3.10**:



3.10 **3.11** **3.12**

Scheme 3.6 Synthesis of side-chain **3.11** and by-product **3.12**

a) BnOH, base (NaH or *t*-BuOK), solvent (DME or THF), rt.

Benzyl alkoxide successfully displaced the bromine atom at the sp^3 carbon centre, thereby introducing a benzylated alcohol functionality. Examination of the ^1H NMR spectrum revealed both alkene protons (multiplets, 5.61-5.62 ppm and 5.91-5.93 ppm) and the resonance of the five aromatic protons, which appeared as a multiplet (7.26-7.34 ppm).

However, the formation of the benzylated propargyl alcohol **3.12**, presumably *via* a competing elimination pathway, was inherent to the reaction. The analysis of the ^1H NMR spectrum of this by-product showed again the resonance of the five aromatic protons (multiplet, 7.31-7.38 ppm) but this time a triplet corresponding to the acetylene protons (triplet, 2.47 ppm) confirmed the formation of a mono-substituted triple bond.

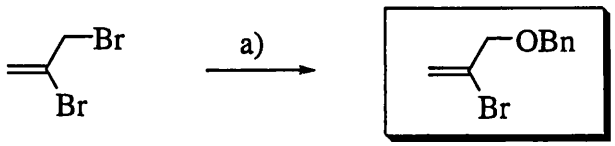
Attempts to influence the outcome of the reaction in favour of alkene **3.11** are summarised in **Table 3.1**:

entry	base	solvent	conversion %	Ratio P:ByP [(a)]
1	NaH	DME	65	2.1:1
2	*t*BuOK	DME	63	2.4:1
3	NaH	THF	61	2.8:1
4	*t*BuOK	THF	72	3:1

Table 3.1: Synthesis of side-chain **3.11**.

(a): ratio product (**3.11**): by-product (**3.12**).

We first turned our attention to 1,2-dimethoxyethane DME, a notoriously good solvent for SN2 processes [13] (entries 1 and 2). The reaction proceeded within an hour and the best P:Byp ratio was obtained with sodium *t*-butoxide (63 %, 2.3:1). Alternatively, when the reaction was performed in THF, the best results were obtained using *t*-butoxide (72 %, 3:1). Although the P:Byp ratio and the conversion were slightly improved, the reaction was much slower (complete after 12 hours). Overall, the choice of the base or ethereal solvent seemed to have little influence on the P:Byp ratio. In a last attempt, we investigated the influence of sodium iodide on the course of the reaction:



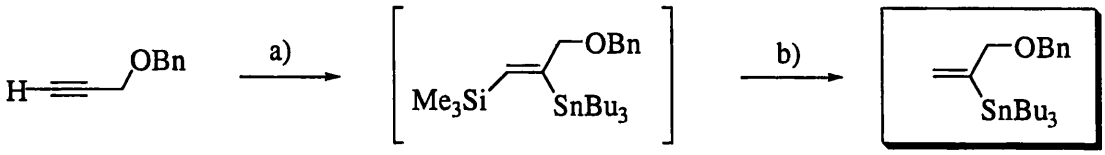
3.10 **3.11**

Scheme 3.7: Synthesis of side-chain **3.11** with sodium iodide

a) BnOH, NaH, NaI (0.3 eq.), THF, rt, 65 %.

This time, side chain **3.11** was formed exclusively in 65 % yield. Replacing the bromine by iodine *via* a Finkelstein type reaction [13] cancelled the competing elimination process and promoted the SN2 substitution. The reaction conditions have not been optimised and higher yield of alkene **3.11** might be obtained with other iodine sources (potassium iodide or tetrabutylammonium iodide) or a different solvent (acetone particularly favours the halogen exchange [13]).

On the other hand, alkyne **3.12** was recycled to the stannylated equivalent of *gem*-alkene **3.11**:



3.12 **3.13** **3.14**

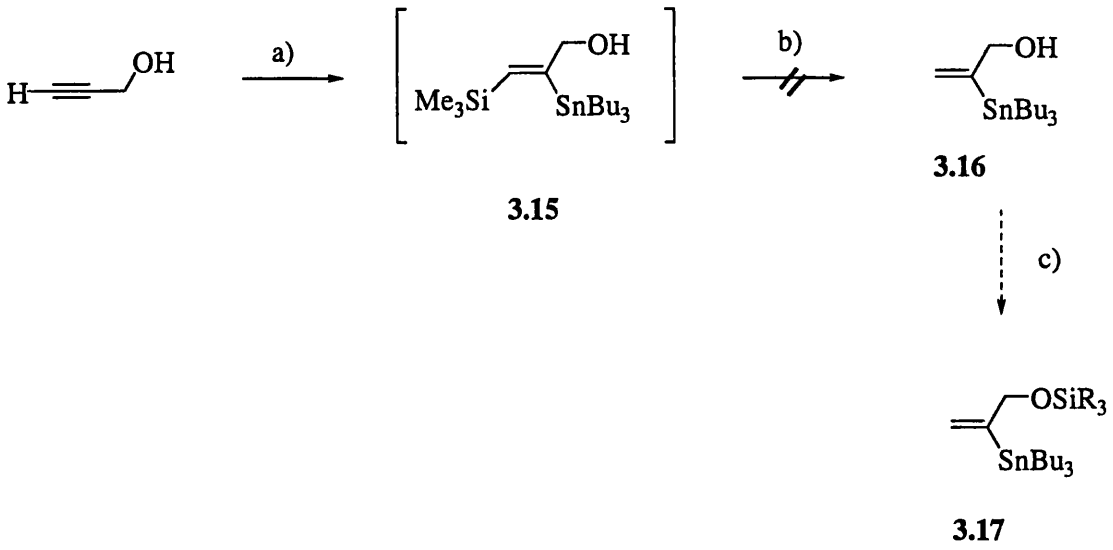
Scheme 3.8: Recycling by-product **3.12** to the *gem*-stannylated alkene **3.14**.

a) $Pd(dba)_2$, PPh_3, $Me_3SiSnBu_3$, THF, reflux, 4 h; b) TBAF, reflux 12 h, 65 % overall yield.

Palladium-catalysed silyl-stannylation of terminal alkyne **3.12** proceeded regioselectively to afford intermediate **3.13** [14]. This intermediate was not isolated

and *in situ* desilylation with tetrabutylammonium fluoride (TBAF) gave 65 % (overall yield) of the *gem*-stannylated alkene **3.14**. By-product **3.12** has then been efficiently recycled into the alternative side-chain **3.14**.

In order to diversify the alcohol-protecting group of the *gem*-alkene side-chain, the same procedure was repeated with commercially available propargyl alcohol:



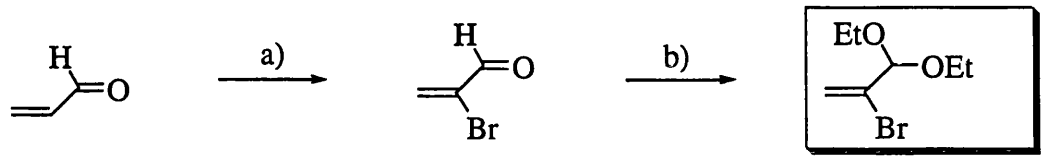
Scheme 3.8: Palladium-catalysed silyl-stannylation with propargylic alcohol.

a) $Pd(dba)_2$, PPh_3, $Me_3SiSnBu_3$, THF, reflux, 4 h, 65 %; b) TBAF, reflux 12 h; c) Et_3N, imidazole, R_3SiCl.

Unfortunately, intermediate **3.15** was the only isolated product: the de-silylation stage with tetrabutylammonium fluoride (TBAF) proved unfruitful, leading to the progressive decomposition of the silyl-stannylated intermediate **3.15** over prolonged reaction time (above 12 h). This result confirmed earlier findings by T. E. Nielsen [15]: silylated alcohols **3.17** are not directly accessible by this method and TBAF slowly decomposes silyl-stannylated alkene **3.15**.

3.12. *Side-chain bearing a protected aldehyde*

Alternatively, we envisaged the synthesis of the *gem*-alkene side chain **3.19**:



3.18 **3.19**

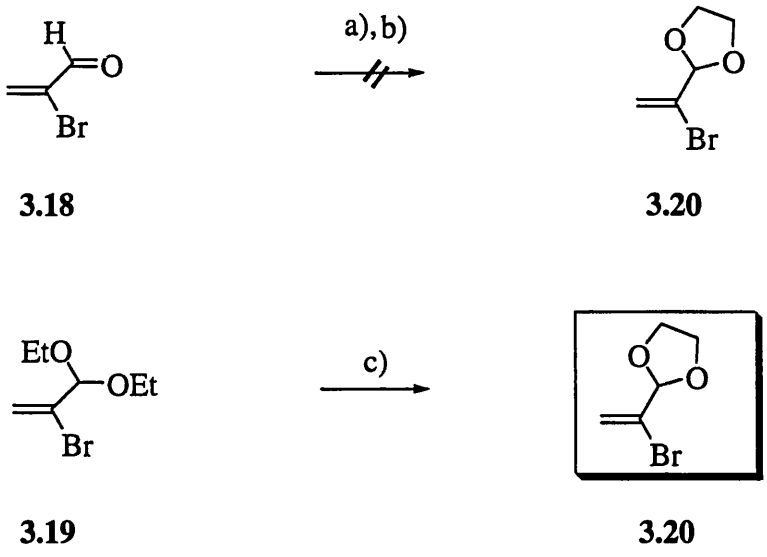
Scheme 3.9: Synthesis of side-chain **3.19**.

a) Br_2, Et_3N, CH_2Cl_2, 0 °C to rt, 60%; b) 10 mol % NH_4NO_3, $HC(OEt)_3$, heat, 60 %.

Our procedure was based on an earlier literature report [16]. However, the bromination-elimination sequence was carried out in dichloromethane with triethylamine in order to avoid the cumbersome steam distillation proposed by A. B. Smith, III *et al* [16]. The reaction proceeded cleanly and was performed on a multi-gram scale. The moderate yield (60 %) reflected the volatility of the 2-bromo-acrolein **3.18**: some material was inevitably lost when concentration *in vacuo* was attempted. The subsequent acetalisation was uneventful and completely followed the previously reported procedure. After Kugelrhor distillation (bp 83-85 °C, 6 mmHg), the acyclic acetal **3.19** was obtained in 60 % yield from a six-gram scale reaction. Analytical data was identical to that previously reported [16].

It is noteworthy that the success of the acetalisation procedure depends on the strength of the acid employed: a weak acid such as ammonium nitrate was required in order to avoid the polymerisation of 2-bromo-acrolein **3.18** [16].

Although acetal **3.19** has proven to be stable in the presence of organometallic reagents such as homocuprates [17], the synthesis of the more resistant cyclic acetal **3.20** was also investigated to provide a potential alternative:



Scheme 3.10: Synthesis of cyclic acetal **3.20**.

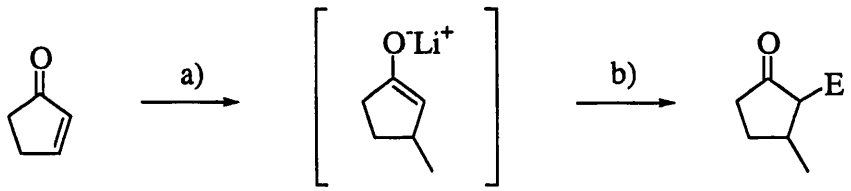
a) 10 mol % *p*-TSA, ethylene glycol, THF, reflux; b) 10 mol % NH_4NO_3, ethylene glycol, THF, reflux; c) ethylene glycol, $CeCl_3.7H_2O$, heat, 52 %.

We soon realised that classic acetalisation procedures with *para*-toluene sulfonic acid (*p*-TSA) or even ammonium nitrate and ethylene glycol in tetrahydrofuran consistently led to polymerised material. Furthermore, a former report accounts for the success of the same acetalisation but the procedure inconveniently requires the use of dry HBr gas [18]. However, a transacetalisation procedure from open acetal **3.19** in the presence of cerium trichloride heptahydrate ($CeCl_3.7H_2O$) in neat ethylene glycol led to the formation of the desired cyclic acetal **3.20** in 52 % maximum yield. Nevertheless, it was found that the yield of the reaction was inconsistent and ranged from 20 % to 52 %.

3.2. 1,4-Addition and further enolate trapping employing organocuprate reagents

3.21. *1,4-Addition with dimethylcuprate: in search of an electrophile for the enolate trapping*

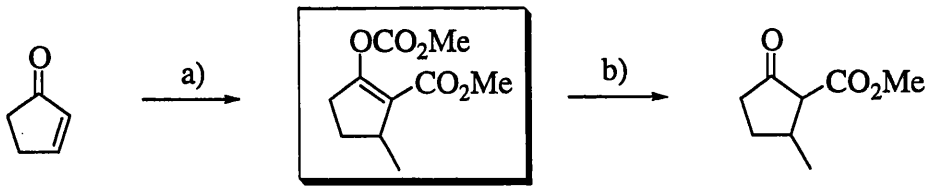
First investigative studies were carried out on cyclopentenone using the well-known Gilman reagent, dimethylcuprate **3.5** (Me_2CuLi) in order to introduce the methyl group first. The conjugate addition in itself is well documented [8] and should allow an appropriate screening of electrophiles for the trapping of the resulting enolate:



Scheme 3.11: First investigative studies: in search of a suitable electrophile.

a) Me_2CuLi, Et_2O, -78 °C; b) E = Electrophile (H_2CO, DMF, HCOEt, *N*-formylpiperidine, $ClCO_2Me$).

Reactions with monomeric formaldehyde were first envisaged. However, the problematic cracking of paraformaldehyde and subsequent co-distillation with tetrahydrofuran rendered the process impractical [19] [11]. Furthermore, despite our numerous attempts, the non-formylated 1,4 adduct was consistently exclusively recovered. Formylation reaction with dimethylformamide DMF, formyl piperidine [20] or ethyl formate also gave disappointing results: the presumed enolate anion did not react with any of these electrophiles.



3.21 **3.22**

Scheme 3.12: Successful 1,4-addition/enolate trapping with methyl chloroformate.

a) i: Me_2CuLi, Et_2O, -78 °C, ii: $ClCO_2Me$, -78 °C, Et_2O, 45 %; b) MeONa, MeOH, 95 %.

Finally, methyl chloroformate successfully C-alkylated the resulting enolate. As previously described [21], concomitant O-alkylation took place and the isolated product was in fact enol ester carbonate **3.21** in 45 % yield along with some of the 1,4 adduct (less than 5 %). The inspection of the ^1H NMR spectrum revealed the presence of both methoxy groups (singlets, 3.66 ppm and 3.81 ppm) as well as the methyl group (doublet, 1.12 ppm). ^{13}C NMR analysis accounted for the resonance signals of the carbons from the ester and carbonate moiety (158.77 ppm and 163.91 ppm); both functionalities also gave characteristic bands in the IR spectrum (1768 cm^{-1} and 1709 cm^{-1}).

The addition of polar additives such as HMPA and DMPU did not alter the course of the reaction: the same enol ester carbonate product **3.21** was obtained, in identical yields.

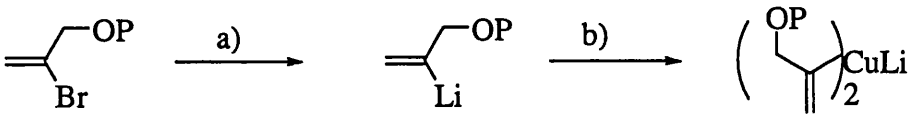
Following literature precedence [21], facile methanolysis of carbonate **3.21** led to β-keto ester **3.22** in 95 % yield. A single methoxy group resonance was observed by ^1H NMR (3.76 ppm) and a new ^{13}C resonance signal appeared in the ^{13}C NMR spectrum (211.49 ppm), accounting for the ketone moiety.

3.22. *1,4-Addition/enolate trapping with side-chains 3.11 or 3.19 and methyl chloroformate*

Studies were carried out with the most readily accessible *gem*-alkenes **3.11** and **3.19** containing an alcohol-protected side-chain and a carbonyl-protected side-chain.

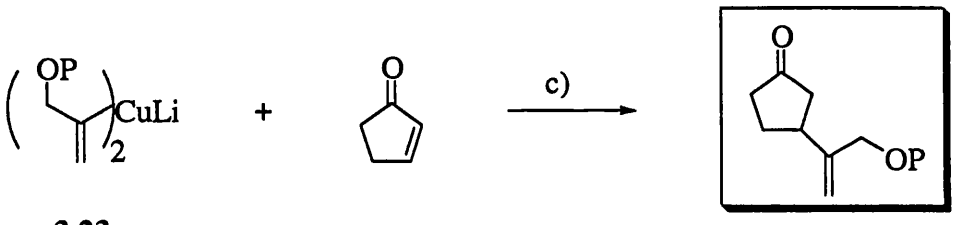
We first decided to limit our investigations to the 1,4-addition only:

Formation of the organocuprate reagent:



3.23

Conjugate addition with cyclopentenone:



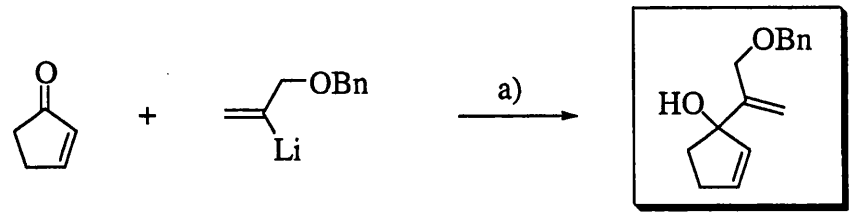
3.23

Scheme 3.13: 1,4-Addition of lithiated side-chains **3.11** and **3.19**: general procedure.

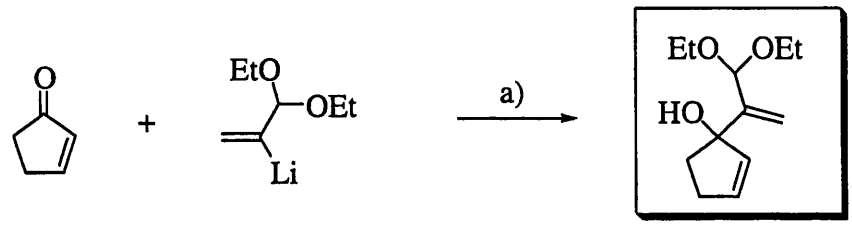
a) *t*-BuLi, Et_2O, -78 °C; b) Copper(I) salt, Et_2O, -78 °C; c) i: Et_2O, -78 °C, ii: NH_4Cl, -78 °C to rt.

Attempts to generate and react the homocuprates **3.23** generated from the lithiated *gem*-alkenes **3.11** or **3.19** and copper iodide (CuI) were unsuccessful: no reaction took place and most of the starting material was recovered. The formation of the organocuprate reagent **3.23** seemed problematic: the reaction medium (at the organocuprate formation stage) was not homogenous and at least part of the copper iodide remained at the bottom of the reaction flask.

Reactions with catalytic amounts of copper iodide were also examined:



3.24



3.25

Scheme 3.14: Reaction with catalytic amount of CuI

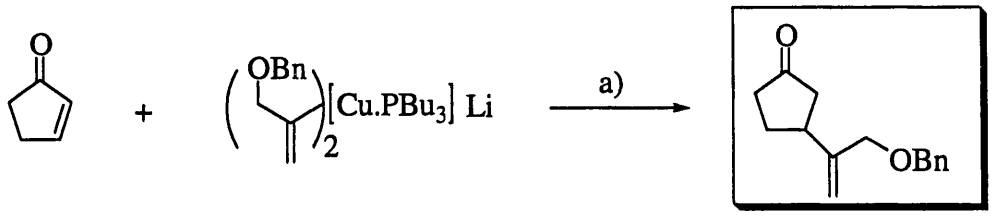
a) 10 mol % CuI, Et_2O, -78 °C, 56 % for **3.24** and 72 % for **3.25**.

In both cases, the 1,2-addition adduct was the only product of the reaction. Tertiary alcohols **3.24** and **3.25** were isolated in 56 % and 72 % yields respectively after flash column chromatography. The absence of a C=O stretch in the IR spectra in conjunction with the lack of a carbonyl resonance signal in the ^{13}C NMR spectra confirmed the outcome of both reactions.

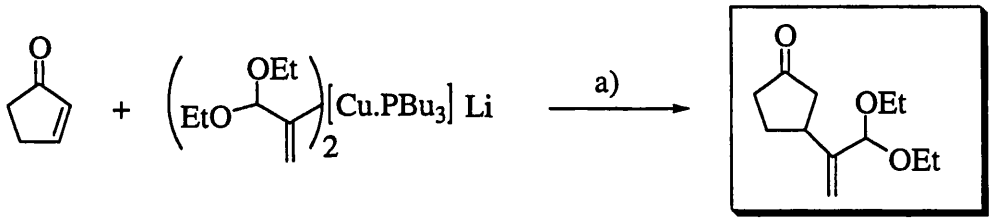
It became apparent that, if the 1,4-additions of the lithiated side-chains **3.11** and **3.19** were to take place, stoichiometric amounts of copper salt were required in order to prevent the formation of 1,2-addition adducts **3.24** and **3.25**.

Noyori *et al*, in their total synthesis of prostaglandins [7], reported the use of another source of $Cu^{(I)}$, copper iodide-tri-*n*-butylphosphine complex $[CuI.PBu_3]_4$. This complex is readily accessible from copper iodide and tri-*n*-butylphosphine [8] and is

soluble in ethereal solvents as opposed to copper iodide, which forms a slurry. Furthermore, the presence of the tri-*n*-butylphosphine ligand (PBu_3) increases the stability of the organocuprate reagent allowing longer reaction times and higher temperatures [8].



3.26 **3.27**



3.28 **3.29**

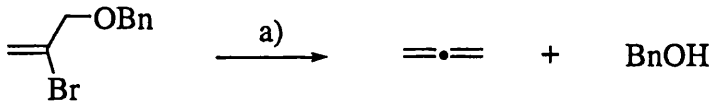
Scheme 3.15: 1,4-addition of side-chains **3.11** and **3.19**.

a) i: Et_2O, -78 °C, ii: NH_4Cl, 45 % for **3.27** and 70 % for **3.29**.

The use of $[CuI.PBu_3]_4$ allowed clean and reproducible formation of both homocuprates **3.26** and **3.28**: clear homogeneous reaction mixtures were obtained (yellow solution for **3.26**, orange solution for **3.28**) which reacted successfully with cyclopentenone to afford ketones **3.27** and **3.29** in 45 % and 70 % yield respectively. Examination of the ^{13}C NMR spectra revealed the resonance signal of the carbon of the carbonyl functionality (218.28 ppm for **3.27**, 218.41 ppm for **3.29**); in combination, two strong bands were recorded in the IR spectra corresponding to the

C=O vibration (1741 cm^{-1} for **3.27**, 1736 cm^{-1} for **3.29**). The analysis of the ^1H NMR spectrum of acetal **3.29** showed two distinct and close triplets for the methyl protons (1.22 for CH_{3A}, 1.23 CH_{3B}) and two multiplets for the methylene protons of the acetal moiety (3.42-3.50 ppm CH_{2E}, 3.57-3.65 ppm CH_{2F}) reflecting the diastereotopic relationship in between both ethoxy groups. On the other hand, the presence of the benzyl functionality of ketone **3.27** was confirmed by the ^1H NMR spectrum, which showed the resonance of five aromatic protons of the benzyl functionality as a multiplet (7.27-7.38 ppm).

Ketone **3.27** was obtained in much lower yield than its analogous compound **3.29**. Investigative studies were carried out on the lithiation of side-chain **3.11** itself:



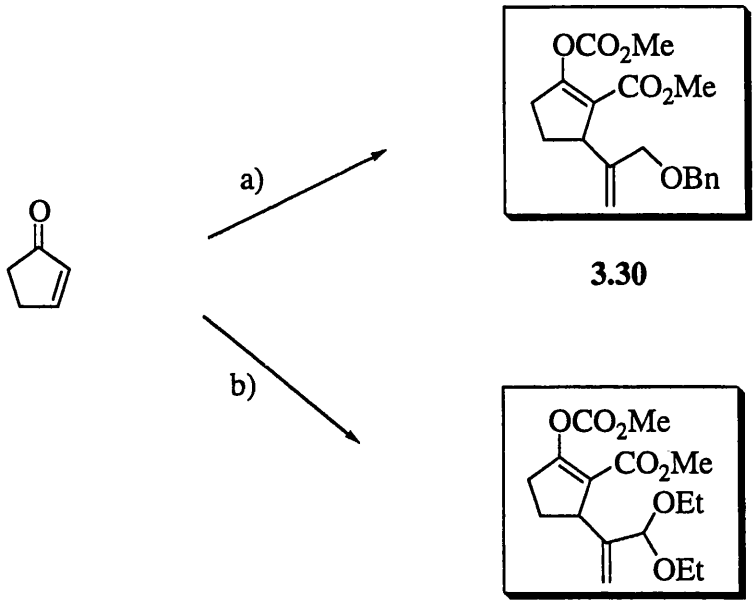
3.11

Scheme 3.16: Proposed decomposition pathway of the lithiated side-chain **3.11**.

a) i: *t*-BuLi, Et_2O, -78 °C, ii: H_2O, -78 °C to rt.

We soon discovered that the lithiated side-chain was unstable: substantial amounts of benzyl alcohol were consistently recovered after simple lithiation studies followed by quenching with water. The formation of allene gas is believed to be the driving force of the decomposition pathway. Thus, unsurprisingly, the reactions involving lithiated *gem*-alkene **3.11** gave lower yields than those obtained with the lithiated counterpart **3.19**.

Nevertheless, taking advantage of the above results, the 1,4-addition/enolate-trapping strategy was subsequently investigated.



3.30

3.31

Scheme 3.17: 1,4-Addition/enolate trapping with side chains **3.11** and **3.19**.

a) i: organocuprate **3.26**, Et_2O, -78 °C, ii: $ClCO_2Me$, 25 % overall yield; b) i: organocuprate **3.28**, Et_2O, -78 °C, ii: $ClCO_2Me$, 60 % overall yield.

After enolate trapping with methylchloroformate, enol ester carbonates **3.30** and **3.31** were obtained in 25 % and 60 % yield respectively. The 1,4 adducts **3.27** or **3.29** were not detected. The ^{13}C NMR spectra analysis revealed the resonance signals for carbons of two carbonyl groups (160.05 and 163.28 for **3.30**, 160.64 ppm and 163.57 ppm for **3.31**) confirmed by IR analysis (1766 cm^{-1} and 1742 cm^{-1} for **3.30**, 1769 cm^{-1} and 1714 cm^{-1} for **3.31**). Again, the diastereotopic nature of the ethoxy groups of the acetal **3.31** is reflected in the corresponding ^1H NMR spectrum showing two distinct triplets for the methyl protons (1.20-1.24 ppm and 1.22-1.25 ppm) and two distinct multiplets for the methylene protons (3.57-3.66 ppm and 3.72-3.77 ppm). Similarly, the diastereotopic benzylic protons of enol carbonate ester **3.30** gave two distinct doublets (4.45 ppm and 4.56 ppm). In both ^1H NMR spectra, two singlets

accounted for the presence of the methoxy group (3.66 ppm and 3.89 ppm for **3.30**, 3.67 ppm and 3.90 ppm for **3.31**)

3.23. *Recapitulative analysis*

The results of the 1,4-addition/enolate trapping strategy are summarised in the table below:

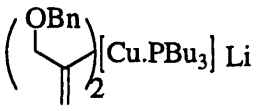
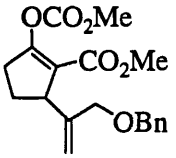
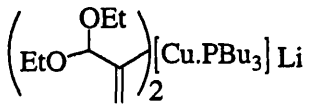
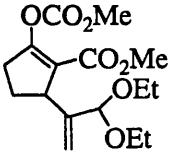
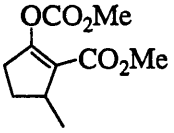
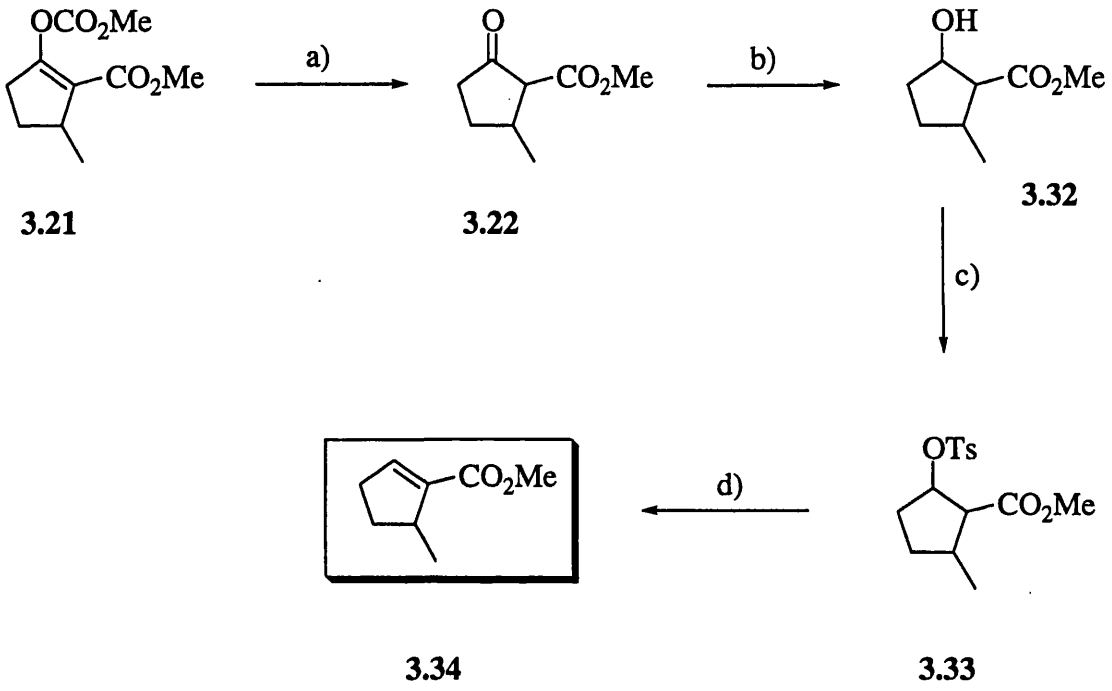
entry	organocuprate	product	yield %
1			25
2			60
3	Me_2CuLi		45

Table 3.2: Recapitulative table

Enol ester carbonate **3.31** (entry 2) was synthesised in better yields than its counterpart **3.30** (entry 1) due, at least in part, to the instability of the lithiated side chain **3.11**. On the other hand the readily accessible enol ester carbonate **3.21** (entry 3) offers another possible synthetic route. We then decided to carry on with further investigative studies from either enol ester carbonate **3.21** or enol ester carbonate **3.31**.

3.3 Two synthetic routes towards ring A

The introduction of the side-chain was theoretically envisaged *via* a new 1,4-addition involving unsaturated ester **3.34**. Therefore, we embarked on the synthetic strategy depicted below:

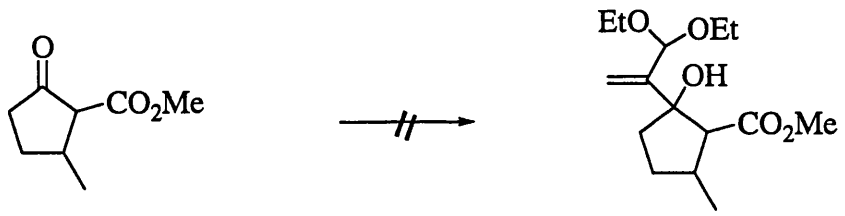


Scheme 3.18: First synthetic strategy form enol ester carbonate **3.21**.

a) MeONa, MeOH, 2 h, rt, 95 %; b) $NaBH_4$, MeOH, 1 h, 0 °C, 70 %; c) TsCl, Pyr., 3 days, rt; 60 %; d) DBU, DMF, 80 °C, 1 h, 75 %.

As it was seen before, methanolysis of the enol ester carbonate **3.21** with sodium methoxide/methanol afforded 95 % of keto ester **3.22**.

En route towards unsaturated ester **3.34**, the possibility of introducing side-chain **3.19** *via* a nucleophilic attack on the carbonyl moiety of keto ester **3.22** was also considered:



3.22 **3.35**

Scheme 3.19: Unsuccessful nucleophilic attack on keto ester **3.22**.

However, disappointing results were obtained, even with the stable lithiated side-chain **3.19**: starting keto ester was invariably recovered, no reaction took place. The basic character of the organolithium reagent was probably incompatible with the acidic proton in the α-position of both carbonyl groups. It is believed that lithiated side-chain **3.19** acted as a base, resulting in the formation of a stabilised enolate, which re-pronated during the aqueous work-up. Furthermore, the corresponding Grignard reagent could never be formed: vinyl bromide **3.19** did not react with magnesium turnings, in Et_2O or THF, with or without initiators (iodine crystals, dibromoethane). Organocerium reagents, owing to their low basicity, are usually a good alternative in such situations [22]. In the present case however, no reaction was observed and the formation of the organocerium derivative was never clearly ascertained.

Studies towards the direct nucleophilic attack on keto ester **3.22** were abandoned: our efforts were then concentrated on the synthetic pathway described in **Scheme 3.18**. From keto ester **3.22**, reduction with sodium borohydride in methanol led to alcohol **3.32** in 70 % yield. Interestingly, the resulting eight isomers could be separated into two distinct sets by flash chromatography. The ^1H NMR spectra contained a new resonance signal (apparent broad singlet, 4.44 ppm for the minor set, multiplet, 4.37-4.42 ppm for the major set) accounting for the reduced carbonyl functionality. In

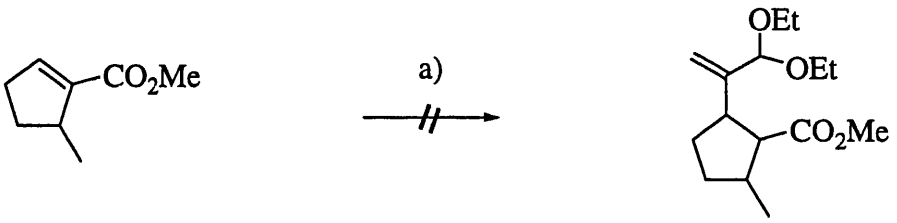
conjunction, the ^{13}C NMR spectra analysis revealed a new CH resonance signal (76.55 ppm for the minor set, 74.50 ppm for the major set) and the absence of the quaternary carbonyl carbon of the ketone functionality.

Surprisingly, hydroxy ester **3.32** was not readily dehydrated: the tosylation of the hydroxy moiety in neat pyridine was required in order to proceed *via* a β-elimination process. Unsaturated ester **3.34**, which would have been the result of a subsequent elimination reaction, was not formed and in fact, tosylated alcohol **3.33** was the only product (60 % yield). Although the two sets of diastereoisomers were clearly differentiated by NMR spectroscopy, they could not be separated at this stage. ^{1}H NMR examination accounted for the presence of the tosyl functionality: a sharp singlet for the resonance of the methyl protons (2.44 ppm for the minor set, 2.45 ppm for the major set) and the typical AA'BB' resonance pattern for the four aromatic protons (two apparent doublets 7.32-7.34 ppm and 7.74-7.76 ppm for the minor set, two other apparent doublets 7.26-7.35 ppm and 7.76-7.78 ppm for the major).

Finally, the β-elimination was performed in dimethylformamide (DMF) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base. Although the same reaction could be performed in tetrahydrofuran (THF) with sodium *t*-butoxide, the former method was preferred, giving generally much cleaner results. Unsaturated ester **3.34** was not very stable and needed to be kept at low temperature (≤ 5 °C) in order to avoid decomposition. Compared with its precursors, the ^{1}H NMR spectrum of unsaturated ester **3.34** was simplified owing to the expected disappearance of any diastereomeric relationship. The resonance of the alkene proton of the conjugated double bond gave rise to an apparent multiplet (6.72-6.74 ppm). ^{13}C NMR analysis accounted for the quaternary carbons of this new double bond (140.84 ppm and 143.17 ppm) and in general, spectroscopic data compared favourably with a closely related literature compound [23]. It has to be noted that any attempt to obtain suitable mass

spectrometric data of the unsaturated ester from any available ionisation sources (EI, CI, FAB, ES) failed: neither the molecular ion nor any of the ions accounting for an obvious fragmentation could be detected.

The introduction of the side-chain **3.19** was then investigated:



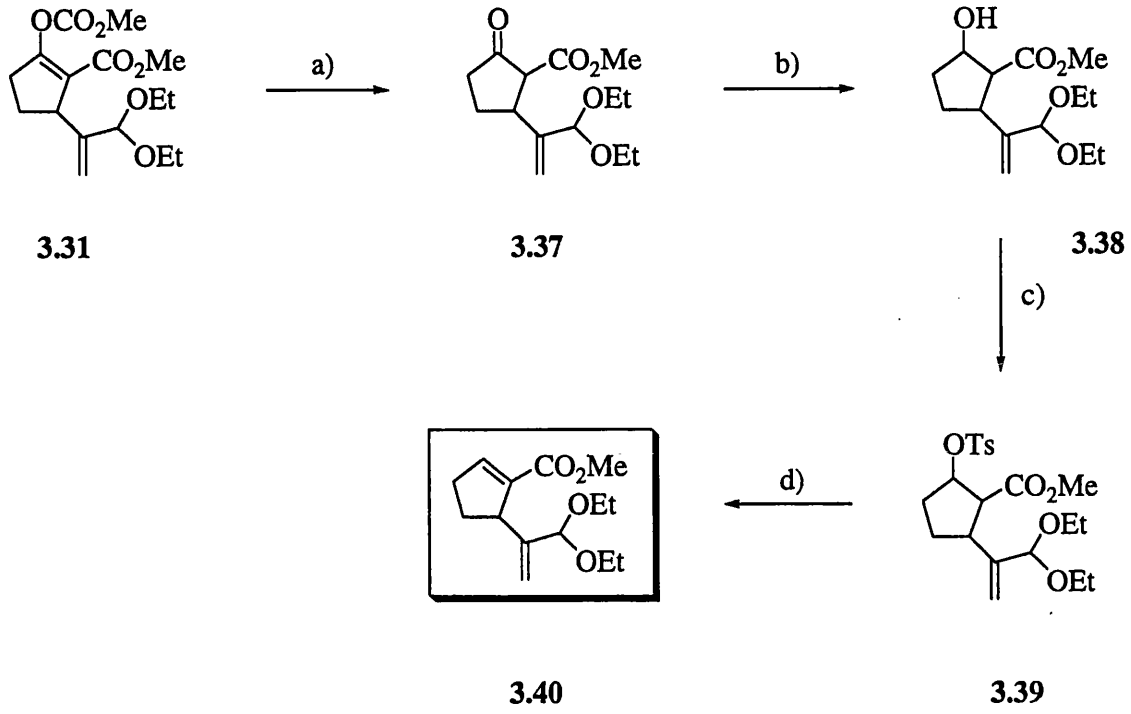
3.34 **3.36**

Scheme 3.20: 1,4-Addition of side-chain **3.19** with unsaturated ester **3.34.**

a) organocuprate **3.28**, Et_2O or THF, -78 °C.

Despite an encouraging literature report on a related system [24], the conjugate addition failed to produce ester **3.36**. The starting unsaturated ester **3.34** was recovered in its totality and the change in solvent from Et_2O to THF had no positive influence on the outcome of the reaction.

Instead, we reasoned that the side chain had to be introduced first, *via* a 1,4-addition reaction on cyclopentenone. The introduction of the methyl group would then take place from unsaturated ester **3.40**. Therefore, a second synthetic route was promptly designed:

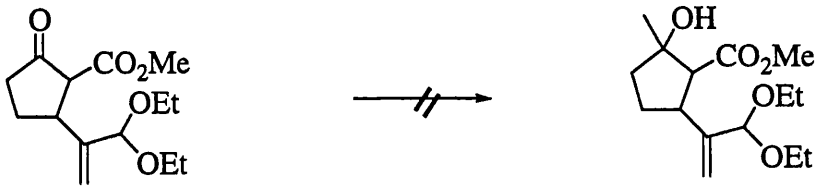


Scheme 3.21: Second strategy from enol ester carbonate **3.31**

a) MeONa, MeOH, 2 h, rt, 95 %; b) $NaBH_4$, MeOH, 1 h, 0 °C, 83 %; c) TsCl, Pyr., 3 days, rt; 66 %; d) DBU, DMF, 80 °C, 1 h, 66 %.

As in the first synthetic approach, keto ester **3.37** was easily accessible from enol ester carbonate **3.31** and sodium methoxide in methanol (95 % yield). A single methoxy group resonance was observed by ^1H NMR (singlet, 3.74 ppm) and a new ^{13}C resonance signal appeared in the ^{13}C NMR spectrum (210.72 ppm), accounting for the ketone moiety.

At this stage, introduction of the methyl group *via* a nucleophilic attack on keto ester **3.37** was also envisaged:



3.37 3.41

Scheme 3.22: Unsuccessful nucleophilic attack on keto ester **3.37**.

Once again however, this strategy completely failed to produce tertiary alcohol **3.41** or any other product. Keto ester **3.37** was always recovered in its totality, whether methyllithium (MeLi) or methylmagnesiumbromide (MeMgBr) were reacted in diethyl ether or tetrahydrofuran even at room temperature for up to six hours. Employing several equivalents of the organometallic reagent (up to four in the case of MeMgBr) did not alter the course of the reaction and it was again acknowledged that a direct nucleophilic attack on keto ester **3.37** was not a productive strategy. Therefore, investigative studies went on, along the proposed synthetic pathway (**Scheme 3.21**).

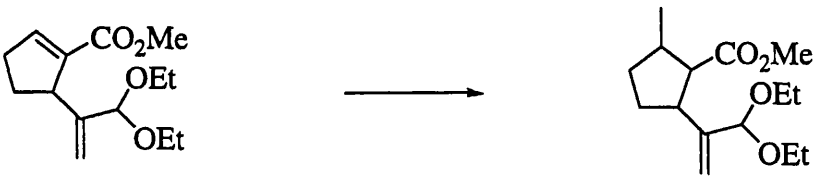
Reduction with sodium borohydride in methanol proceeded uneventfully in 83 % yield to provide hydroxy ester **3.38**. This time however, the diastereoisomers could not be separated from each other. The resulting NMR spectra were complicated but unambiguously accounted for the reduction of the ketone functionality: the resonance signal of a new proton (apparent multiplet, 4.38-4.51 ppm) in the ^{1}H NMR spectrum in combination with the resonance signal of a new CH carbon (74.53 ppm) in the ^{13}C NMR spectrum and the typical (O-H) broad absorption band in the IR spectrum (3458 cm^{-1}) indicated the presence of the alcohol functionality.

The hydroxy ester **3.38** was further tosylated with *p*-toluenesulphonyl chloride in neat pyridine to afford tosylated ester **3.39** in 66 % yield after purification. The

diastereoisomers were not separable but, for the resonance of a few protons or carbons, two distinct sets were sometimes observed in both NMR spectra. Again, examination of the ^{1}H NMR spectrum revealed the presence of the tosyl functionality: a sharp singlet for the resonance of the methyl protons (2.45 ppm for the minor set, 2.44 ppm for the major set), the typical AA'BB' resonance pattern for the four aromatic protons (two apparent doublets 7.26-7.35 ppm and 7.74-7.90 ppm for both sets).

Subsequent elimination with DBU in DMF at 80 °C produced unsaturated ester **3.40** in 66 % yield. The structure of unsaturated ester **3.40** was unequivocally confirmed by NMR spectroscopy: the resonance of the alkene proton of the conjugated double bond gave rise to a triplet of doublets (6.93-6.95 ppm). Analysis of the ^{13}C NMR spectrum accounted for the quaternary carbons of this new double bond, although the assignment was not certain (145.95 ppm and 148.34 ppm).

Finally, the introduction of the methyl group was envisaged. A range of organocuprates was reacted with unsaturated ester **3.40**:



3.40 **3.41**

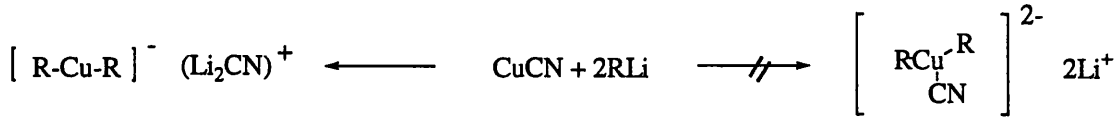
Scheme 3.23: 1,4-Addition with unsaturated ester **3.40**.

At first the simple Gilman reagent Me_2CuLi was reacted with unsaturated ester **3.41**. However, the starting unsaturated ester was recovered in its totality and no product was ever detected by NMR spectroscopy. Two options were investigated: 1,4-

addition with Yamamoto type cuprates ($MeCu.BF_3$ and $Me_2CuLi/BF_3.Et_2O$) [25] and 1,4-addition with higher-order organocuprates ($Me_2CuCNLi_2$) [26].

Yamamoto's cuprates, as it was described **Chapter 2**, show enhanced reactivity due to the presence of the strong Lewis acid BF_3. With our substrate however, $MeCu.BF_3$ failed to promote 1,4-addition and observation of the crude NMR spectroscopic data accounted for the presence of an aldehyde functionality as the only product present along with unreacted starting material. The acetal moiety was not compatible with this type of organocuprate, which promoted partial deprotection of unsaturated ester **3.40**. This observation found echo in the earlier literature [27].

We then turned our attention to the higher-order organocuprate reagent $Me_2Cu(CN)Li_2$ **3.45** [26 8]. As for Yamamoto cuprates, higher-organocuprate reagents have been shown to react where Gilman reagents failed to undergo 1,4-addition. Although the role of the cyano moiety (CN) in this type of reagent remains obscure, the structure of the reagent itself has been recently elucidated, therefore ending a long lasting controversy [28]:



3.42 **3.43**

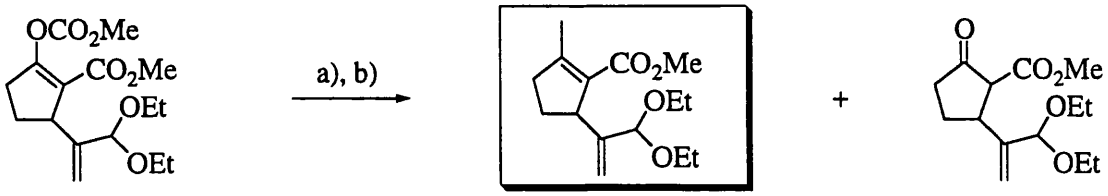
Scheme 3.24: General structure of higher order organocuprates.

It is now acknowledged that the CN group does not remain on the copper atom but acts as a counter ion. Thus, the species present in an ethereal solution correspond to complex **3.42.**

When three equivalents of $Me_2Cu(CN)Li_2$ **3.45** were reacted with unsaturated ester **3.40** in THF at –78 °C for 2 hours and –30 °C for a further hour, nearly no reaction took place and the starting ester remained almost entirely unreacted (crude ^1H NMR). Only traces of a possible product were detected by ^1H NMR (notably a faint doublet, 1.35 ppm); however, its structure could not be ascertained.

3.4. A possible short synthesis of ring A.

A new short entry towards the synthesis of ring A was considered. We reasoned that enol ester carbonate **3.31** contains an α,β-unsaturated ester functionality and a potentially leaving group (carbonate -OCO_2Me) at the β-position. Therefore, introducing the methyl group should be theoretically possible *via* a 1,4-addition/elimination strategy [8]. However this reaction seemed to go against all the odds: the carbonate functionality is known to be incompatible with organocuprate reagents in general [29], the substrate is very hindered (β,β-disubstituted substrate) and, to our knowledge, no such strategy has been reported with a carbonate group acting as a leaving group.



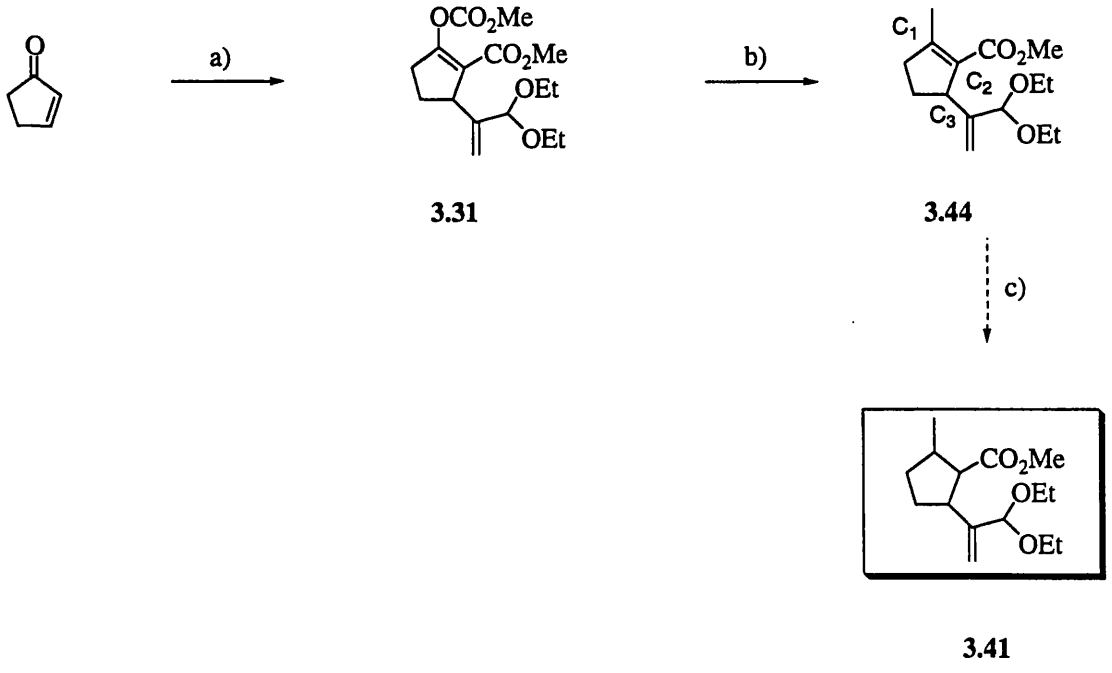
3.31 **3.44** **3.37**

Scheme 3.25: 1,4-Addition elimination strategy from enol ester carbonate **3.31**.

a) Me_2CuLi, Et_2O, -78 °C, 91 % of **3.37**; b) $Me_2CuCNLi_2$, THF, -78 °C, 58 % of **3.37**, 33 % of **3.44**.

When the simple Gilman reagent Me_2CuLi was reacted with enol ester carbonate **3.31** the keto ester **3.37** was the only product of the reaction: simple deprotection occurred, as it was the case earlier with sodium methoxide.

Nevertheless, while proceeding further with the higher-order organocuprate **3.45**, unsaturated ester **3.44** was formed in 33 % yield (alongside with keto ester **3.37**, 58 % yield). The ^1H NMR spectrum analysis accounted for the newly introduced methyl group (2.50 ppm) and although complete ^{13}C NMR data could not be obtained, the detection of the molecular ion (M^+ 269.1) by mass spectroscopy unequivocally confirmed the structure of unsaturated ester **3.44**. Although this latest result needs to be improved to be viable, it offers an attractively short entry to ring A:



Scheme 3.26: A short entry towards ring A.

a) i: organocuprate **3.28**, Et_2O, -78 °C, ii: $ClCO_2Me$, 60 % overall yield; b) $Me_2CuCNLi_2$, THF, -78 °C 33 % yield; c) $NaBH_4$, 1 mol % $CoCl_2$, EtOH/DMF.

From 2,3-cyclopentenone, only two steps would be required to access unsaturated ester **3.44**. Then, cobalt mediated selective reduction of the conjugated double bond

30 would afford ring A in not more than three synthetic steps. Furthermore, performing the reduction of the double bond in the presence of a chiral catalyst 30 would enable us to control the stereochemistry at C_1 and C_2. Alternatively, if the stereochemistry at C_3 was already fixed, the reduction could possibly be carried out diastereoselectively without resorting to the use of a chiral catalyst.

This concise approach has yet to be fully developed. The encouraging results obtained on the 1,4-addition/elimination reaction could open an unprecedented short entry to polysubstituted ring systems in general.

3.5 References

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Chapter 4:

Experimental

4.1 General procedures

^{1}H NMR spectra were recorded on JEOL 270 EX, JEOL 400 EX or a Bruker AM-300 spectrometer at 270 MHz, 400 MHz and 300 MHz respectively. Residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) or TMS (δ_H = 0 ppm) were used as internal references. Coupling constants were measured in Hz. ^{19}F NMR spectra were recorded on a JEOL 400 EX at 376 MHz. ^{13}C spectra were recorded in $CDCl_3$, unless otherwise stated, at 100 MHz, 75 MHz and 67.5 MHz on JEOL 400 EX, Bruker AM-300 and JEOL 270 EX spectrometers respectively, using the resonance of $CDCl_3$ (δ_C = t, 77 ppm) as the internal reference. Infra red spectra were recorded in the range of 4000-600 cm^{-1} on a Perkin Elmer FT 1000 spectrometer with internal calibration. Mass spectra were carried out at Bath University (Finnigan MAT 8340 instrument). Melting points were measured on a Büchi 535 melting point apparatus and are uncorrected. Separation of diastereoisomers was achieved by chiral GC on a SUPELCO™ Betadex 120 column using samples dissolved in dichloromethane in a concentration of 2 mg/mL.

Analytical thin layer chromatography was carried out using glass-backed plates coated with Merck Kieselgel 60 GF_{254} or aluminium backed plates coated with Merck G/UV_{254}. Plates were visualised under UV light (at 254 nm) or by staining with potassium permanganate, vanillin or cerium ammonium molybdate followed by heating. Flash chromatography was carried out using either Merck 60 H silica or Merck Florisil®. Samples were pre-absorbed on silica or loaded as saturated solutions in an appropriate solvent.

Tetrahydrofuran and ether were distilled from sodium with benzophenone ketyl, and DCM and *N*,*N*-dimethylformamide from CaH_2 all under nitrogen. Dry MeOH 99.9%

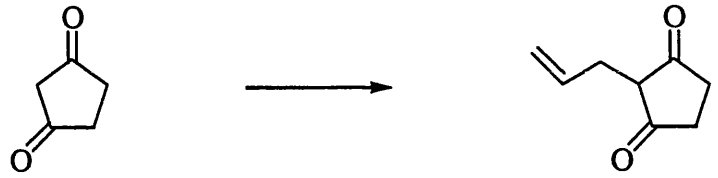
was purchased from Aldrich in a Sure-Seal bottle. Light petroleum refers to petrol bp 40-60 °C, ether refers to diethyl ether.

Preparation of silver nitrate-impregnated silica for the chromatographic separation of monocyclic and bicyclic compounds from RCM reaction [1]: Reagents, silica, MeCN and $AgNO_3$, were used in a ratio of 3:3:1, w:v:w, respectively. A solution of $AgNO_3$ (for example, 5 g) in MeCN (15 mL) was added to silica (15 g). The moist silica was mixed thoroughly for 5 min, the vessel covered with aluminium foil and dried in a hot oven (70 °C) for 4 h. The dry, silver-doped silica was stored in a dark place. **Preparation of silver nitrate-impregnated silica TLC plates [1]:** Reagent ratio was $AgNO_3$:MeCN, 1:3 w:v. Glass-backed silica TLC plates, cut to appropriate sizes, were soaked in a solution of $AgNO_3$ (for example, 1 g) in MeCN (3 mL) for 5 min and then dried in a hot oven for 5-10 min. The dry, silver-doped plates were covered in aluminium foil and stored in the dark. Compounds on the TLC plate were observed using PMA stain and then heating.

Unless otherwise stated, commercially available starting materials were used throughout without any further purification. Copper(I) iodide was purified by precipitation from a saturated aqueous solution of potassium iodide [2]. Copper(I) iodide-tri-*n*-butylphosphine complex was prepared from copper iodide CuI and *n*-tributylphosphine *n*-Bu_3P [2]. Sodium methoxide and sodium *t*-butoxide were freshly prepared from sodium with methanol and *t*-butanol respectively. Tosyl chloride was purified by recrystallisation from light petroleum ether. Reactions requiring anhydrous conditions were performed under nitrogen in flame-dried apparatus. All temperatures quoted are external.

4.2 Chapter 2 experimental.

Preparation of 2-Allyl-cyclopentane-1,3-dione 2.10 [3].



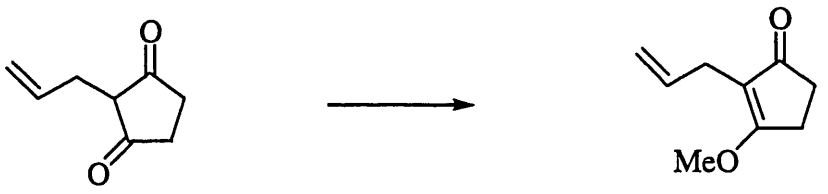
2.6 **2.10**

Palladium allyl chloride dimer $[Pd(allyl)Cl]_2$ (0.09 g, 0.25 mmol, 2.5 mol%)[‡] was added to dppe (0.40 g, 1.00 mmol) in a reaction flask equipped with a nitrogen line and a water condenser. The reaction flask was purged with nitrogen. The solid reagents were dissolved in THF (25 mL) and allyl acetate (1.1 mL, 10.00 mmol) was added. To the yellow-orange solution were added 1,3-cyclopentanedione **2.6** (1.50 g, 15.30 mmol), BSA (3.70 mL, 15.00 mmol) and NaOAc (0.05 g, 0.25 mmol) sequentially. The mixture was heated at reflux for 24 h, after which time it was cooled to room temperature, diluted with MeOH (20 mL) and stirred for 15 min. The cream precipitate was removed by filtering the suspension through a pad of celite®. The pad was washed with more MeOH (3 × 10 mL) and the combined washings were reduced to about a third of the original volume, under reduced pressure. Silica

[‡] The commercially available greenish-yellow Pd dimer was purified by dissolving in a small quantity of warm CH_2Cl_2. This solution was then passed through a small column of silica, which was rinsed several times with CH_2Cl_2. The combined washings were then evaporated to give a bright yellow solid.

(4 g) was added to the concentrate and solvent evaporated. The pre-adsorbed crude mixture was purified by chromatography (SiO_2, CH_2Cl_2-MeOH, 98:2) to isolate allylated cyclopentanedione **2.10** as an off-white solid which was recrystallised from hot EtOAc as shiny colourless needles (1.19 g, 90 %). Mp 152.9-153.3 °C; R_f (CH_2Cl_2-MeOH, 95:5): 0.27, ν_{max}(KBr)/cm^{-1}; 3414 (O-H), 3077 (=CH), 2970 and 2929 (C-H), 2400 (broad, strong), 1868 (broad, strong), 1675 (C=O), 1640 (C=C); δ_H (270 MHz, CD_3OD): 2.58 (4H, s, CH_2CH_2CO), 2.92 (2H, d, *J* 6.0, CH_2=CHCH_2C), 4.99-5.08 (2H, m, CH_2=CHCH_2C), 5.10 (1H, broad s, OH), 5.87 (1H, ddt, *J* 10.0, 17.2 and 6.0, CH_2=C*H*CH_2C); δ_C (270 MHz, CD_3OD): 26.2 (CH_2, *C*H_2CO), 31.5 (CH_2), 115.1 (=CH_2), 116.6 (Cq), 136.4 (=CH), 199.2 (CO); *m/z* (EI$^+$): 138 (100%, M^+), ($C_8H_{10}O_2$ requires *M*, 138.0681. Found: M^+, 138.0680); ($C_8H_{10}O_2$ requires C, 69.5; H, 7.3. Found: C, 69.3; H, 7.3).

Preparation of 2-Allyl-3-methoxy-cyclopent-2-enone 2.5 [3].

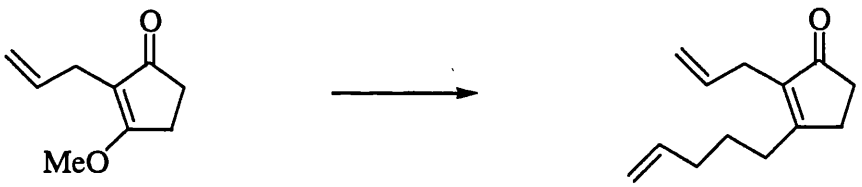


2.10 **2.5**

Conc. H_2SO_4 (4 mL) was added to a solution of 2-allyl-1,3-cyclopentanedione **2.10** (10.00 g, 0.07 mol) and $(MeO)_3CH$ (45.90 mL, 0.42 mol) in MeOH (140 mL). The mixture was heated at reflux for 1 h and after cooling to room temperature, most of the MeOH was carefully removed under vacuum. The residue was brought to pH 8 with saturated sodium hydrogen carbonate solution and extracted with Et_2O (6 × 200 mL). The combined extracts were dried (Na_2SO_4) and solvent removed under

reduced pressure. The residual brown oil was eluted with Et_2O through a column of silica, pre-basified with Et_3N, to afford methyl enol ether **2.5** as a yellow brown oil (7.10 g, 64 %) which was stored under an atmosphere of nitrogen below 5 °C. R_f (Et_2O): 0.12; ν_{max}(film)/cm^{-1}: 3483 (w), 3078 (=CH), 2952 (C-H), 1686 (C=O), 1625 (C=C), 1360 (s), 1261 (s); δ_H (400 MHz, $CDCl_3$): 2.45-2.47 (2H, m, CH_2), 2.68 (2H, t, *J* 4.6, CH_2), 2.90 (2H, d, *J* 6.4, H_2C=CHCH_2C), 3.96 (3H, s, OMe), 4.93-5.03 (2H, m, CH_2CH=CH_2), 5.83 (1H, ddt, *J* 6.3, 10.0 and 17.1, CH_2CH=CH_2); δ_C (400 MHz, $CDCl_3$): 24.6 (CH_2), 25.5 (CH_2), 33.3 (CH_2), 56.4 (CH_3), 114.7 (=CH_2), 118.0 (Cq), 134.9 (=CH), 184.9 (COMe), 204.2 (CO); *m/z* (EI$^+$): 152 (100%, M$^+$), 137 (47, M$^+$ - Me); ($C_9H_{12}O_2$ requires *M*, 152.0837. Found: M$^+$, 152.0833).

Preparation of 2-Allyl-3-pent-4-enyl-cyclopent-2-enone 2.4 [3].

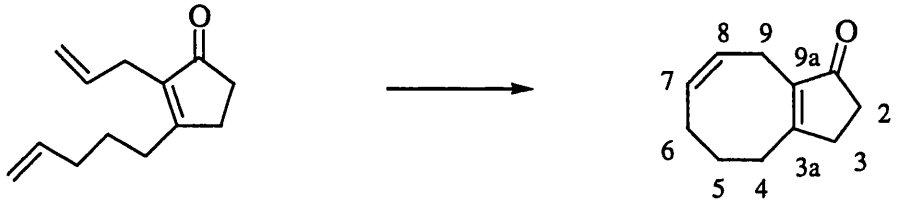


2.5 **2.4**

Magnesium turnings (84 mg, 3.40 mmol) in a 3-necked, 25 mL round bottom flask equipped with a water condenser, were mechanically stirred under nitrogen for 2 h and then suspended in dry Et_2O (7 mL). 5-Bromopentene (0.39 mL, 3.28 mmol) was then added dropwise. Initially, about 0.1 mL was added and the mixture gently heated at reflux for 5 min, after which time the reflux was maintained simply by the addition of remaining 5-bromopentene. On completion, the reagent mixture was stirred at room temperature for 15 min, cooled to 0 °C, and a solution of methylenol ether **2.5** (0.25 g, 1.60 mmol) in Et_2O (2 mL) was added dropwise. The resulting

yellow-brown suspension was stirred at room temperature for eight hours, and then quenched very carefully with 2 M HCl (10 mL). The solution was stirred at room temperature for a further 30 min. The mixture was poured into water and extracted with Et_2O (4 × 15 mL). The combined extracts were dried (Na_2SO_4), the solvent evaporated under reduced pressure and the residue purified by chromatography (SiO_2, CH_2Cl_2) to afford *triene* ***2.4*** as a yellow oil (0.19 g, 62 %). R_f (CH_2Cl_2): 0.2; ν_{max}(neat)/cm^{-1}: 3078 (=CH), 2928 (C-H), 1698 (C=O), 1641 (C=C); δ_H (400 MHz, $CDCl_3$): 1.59-1.71 (2H, m, CH_2), 2.07-2.16 (2H, m), 2.39-2.41 (2H, m), 2.44 (2H, t, *J* 7.8), 2.53 (2H, t, *J* 4.6), 2.95 (2H, d, *J* 6.4, H_2C=CHCH_2C), 4.95-5.07 (4H, m, CH_2CH=CH_2), 5.72-5.85 (2H, m, CH_2CH=CH_2); δ_C (400 MHz, $CDCl_3$): 26.5 (CH_2), 27.3 (CH_2), 29.2 (CH_2), 30.6 (CH_2), 33.6 (CH_2), 34.2 (CH_2), 115.2 (=CH_2), 115.4 (=CH_2), 134.9 (=CH), 137.7 (=CH), 138.0 (Cq), 174.8 (Cq), 209.2 (CO); *m/z* (FAB^+): 191 (100%, M^+ + H), ($C_{13}H_{19}O$ requires *M* + *H*, 191.1436. Found: M^+ + H, 191.1439).

Preparation of 2,3,4,5,6,9-Hexahydro-cyclopentacycloocten-1-one 2.3.



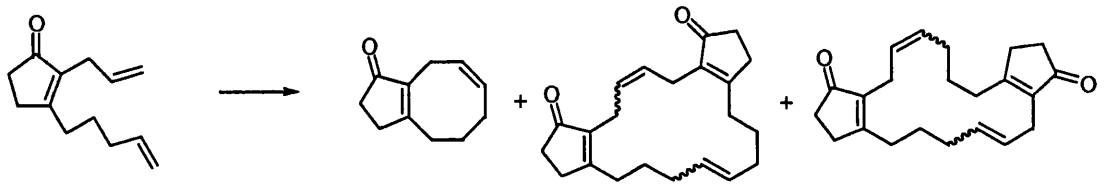
2.4 **2.3**

Employing Ru catalyst **2.14** [3]:

Typical procedure (when Ti(O*i*Pr)$_4$ was used, triene **2.4** and 0.3 equivalent of Ti(O*i*Pr)$_4$ were heated at reflux together for an hour *prior* to the introduction of Ru catalyst **2.14**): a solution of $RuCl_2$(=CHPh)(PCy_3)$_2$ (24 mg, 0.029 mmol, 10 mol%)

in dry, degassed CH_2Cl_2 (0.5 mL), was added *via* a cannula to a solution of triene **2.4** (55 mg, 0.29 mmol) in dry, degassed CH_2Cl_2 (29 mL). The reaction flask was placed in an oil bath and the light purple solution ([triene] = 0.01 M) was heated at reflux for 36 h. The solvent was removed under reduced pressure and the dark residue was chromatographed (SiO_2, light petroleum-Et_2O, 92:8) to afford a mixture of monocycle **2.4** and bicycle **2.3** as an oil (yield: 20 mg; ratio monocycle:bicycle 1:8.0); R_f (light petroleum ether:Et_2O, 92:8): 0.11. The mixture of compounds was separated by further chromatography (1 × 10 cm silver-doped silica column) using 1:1 light petroleum:Et_2O as eluent to isolate the *bicycle* **2.3** (15 mg, 32 %) as a pale yellow oil (and Et_2O as eluent to recover unreacted triene **2.4** (2 mg, 3.5 %) R_f (Et_2O, silver-doped silica TLC plate): bicycle 0.68, monocycle 0.42. Bicycle **2.3**: $\nu_{max}(CDCl_3)/cm^{-1}$: 3015 (=CH), 2934 (C-H), 1697 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$): 1.61-1.67 (2H, m, H_5), 2.09-2.17 (2H, m, H_6), 2.35-2.38 (2H, m, H_2), 2.46-2.49 (2H, m, H_3), 2.62 (2H, t, *J* 6.2, H_4), 2.98 (2H, dd, *J* 1.9 and 5.0, H_9), 5.43-5.51 (1H, m, H_7), 5.77 (1H, apparent quintuplet, *J* 5.4, H_8); δ_C (100 MHz, $CDCl_3$): 22.3 (C_5, CH_2), 24.3 (C_9, CH_2), 25.5 (C_6, CH_2), 29.2 (C_4, CH_2), 31.6 (C_3, CH_2), 34.2 (C_2, CH_2), 127.9 (C_8, =CH), 128.6 (C_7, =CH), 140.2 (C_{3a}), 172.6 (C_{9a}), 209.1 (C_1); *m/z* (FAB$^+$): 163.0 (100%, $M^+ + H$), ($C_{11}H_{14}O$ requires *M* + *H*, 163.1123. Found: $M^+ + H$, 163.1127).

Employing Ru catalyst **2.15**:

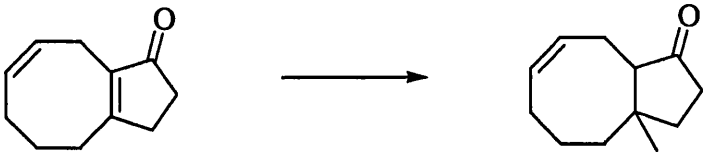


2.4 **2.3** **2.23** **2.24**

Typical procedure (when Ti(O*i*Pr)$_4$ was used, triene **2.4** and 0.3 equivalent of Ti(O*i*Pr)$_4$ were heated at reflux together for an hour *prior* to the introduction of Ru catalyst **2.15**): a solution of Ru catalyst **2.15** (14 mg, 0.016 mmol, 10 mol %) in dry, degassed CH_2Cl_2 (0.5 mL), was added *via* a cannula to a solution of triene **2.4** (31 mg, 0.16 mmol) in dry, degassed CH_2Cl_2 (0.5 mL). The reaction flask was placed in an oil bath and the light purple solution ([triene] = 0.01 M) was heated at reflux for 36 h. The solvent was removed under reduced pressure and the dark residue was purified by chromatography (SiO_2, light petroleum-Et_2O, 92:8) to afford a mixture of *dimer* **2.23** and/or **2.24** (yield: 20 %) and bicycle **2.3** as an oil (yield: 49 %, ratio product:by-product, 2.4:1); R_f (light petroleum ether:Et_2O, 92:8): 0.11. The yield of bicyclic enone **2.3** was determined by ^{1}H NMR spectroscopy. *Dimer* **2.23** and/or **2.24** was separated from bicyclic enone **2.3** by further chromatography (1 × 6 cm silver-doped silica column) using 1:2 light petroleum:Et_2O as eluent. *Dimer* **2.23** and/or **2.24**: R_f: (Silver-doped silica TLC plates, light petroleum-Et_2O, 37:63): 0.21, $\nu_{max}(CDCl_3)/cm^{-1}$: 3021 (=CH), 2919 (C-H), 2859 (C-H), 1695 (C=O), 1622 (C=C), 1442 (sharp), 1403 (sharp), 1273 (sharp), δ_H (400 MHz, $CDCl_3$): 1.57-1.62 (4H, m), 1.80-1.94 (4H, m), 2.17-2.24 (2H, m), 2.41-2.44 (6H, m), 2.52-2.56 (6H, m), 2.65-2.67 (2H, m), 5.77-5.84 (1H, m, =CH), 5.9-6.1 (1H, m, =CH), 6.17 (2H, app. t, *J* 11.9, =CH), δ_C (100 MHz, $CDCl_3$): 21.60, 23.08, 25.08, 26.98, 31.28, 31.39, 31.70,

33.00, 34.47, 34.52, 35.27, 121.00, 117.97, 132.81, 134.46, 135.82, 136.28, 174.22 (C=*C*q), 174.36 (C=*C*q), 208.28 (C=O), 209.15 (C=O), *m/z* (FAB^+): 325.2 (7 %, M^+-H), 163.2 (100 %, [monomer]).

Preparation of 3a-Methyl-2,3,3a,4,5,6,9,9a-octahydro-cyclopentacyclocten-1-one 2.2 [3].

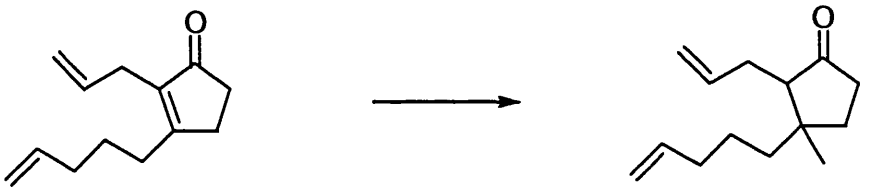


2.3 **2.2**

MeLi (0.37 mL of a 1.5 M solution in Et_2O, 0.55 mmol) was added dropwise to a stirred suspension of CuI (105 mg, 0.55 mmol) in Et_2O (0.6 mL) under nitrogen at -40 °C. After stirring at this temperature for 5 min, the yellow slurry was cooled to -78 °C and $BF_3.Et_2O$ (71 μL, 0.57 mmol) was added. The thick, deep-yellow slurry was stirred for a further 5 min before the dropwise addition of a solution of pre-dried (over 4Å molecular sieve pellets) enone **2.3** (30 mg, 0.18 mmol) in Et_2O (0.2 mL). The mixture was stirred at -78 °C for 5 h, quenched with saturated NH_4Cl solution (3 mL), the phases separated and the aqueous phase re-extracted with Et_2O (5 × 2 mL). The combined organic extracts were dried (Na_2SO_4), the solvent evaporated under reduced pressure and the residue chromatographed (SiO_2). Elution with 99:1 petroleum ether:Et_2O afforded the addition product **2.2** as a yellow oil (17 mg, 53 %) and further elution with 92:8 petroleum ether:Et_2O, gave the unreacted enone **2.3** (13 mg, 43 %). The addition product was isolated as a mixture of isomers with a de of 42% by ^1H NMR and 30% by chiral GC. R_f (light petroleum-Et_2O, 90:10): 0.48;

ν_{max}(neat)/cm^{-1}: 3015 (=CH), 2933 (C-H), 1739 (C=O); δ_H (270 MHz, $CDCl_3$): 0.91 (3H, s, Me minor – 29 %), 1.14 (3H, s, Me, major – 71 %), 1.34-1.61 (2H, m), 1.63-1.86 (5H, m), 1.93-2.17 (1H, m), 2.20-2.49 (5H, m, CHC=CHC*H*$_2$C*H*COC*H*$_2$), 5.54-5.60 (1H, m, C*H*C=CHCH$_2$CHCO), 5.70-5.76 (1H, m, CHC=C*H*CH$_2$CHCO); δ_C (90 MHz, $CDCl_3$): (major isomer) 20.3 (CH_2), 24.6 (CH_2), 24.7 (CH_2), 25.3 (CH_3), 33.8 (CH_2), 34.4 (CH_2), 38.3 (CH_2), 42.3 (Cq), 59.7 (CH), 128.2 (=CH), 129.4 (=CH), 221.9 (C=O), (minor isomer) 16.8 (CH_3), 24.5 (CH_2), 25.0 (CH_2), 26.6 (CH_2), 34.3 (CH_2), 36.7 (CH_2), 37.7 (CH_2), 42.1 (Cq), 63.9 (CH), 129.2 (=CH), 130.7 (=CH), 217.6 (CO); *m/z* (EI$^+$): 178 (100%, M$^+$), 163 (54, M$^+$ - Me), ($C_{12}H_{18}O$ requires *M*, 178.1358. Found: M$^+$, 178.1356); GC (155 °C, 2 mg/mL^{-1}): retention time (% area), 38.47 (3.415), 38.92 (3.435), 39.49 (1.847), 40.38 (1.801).

Preparation of 2-Allyl-3-methyl-3-pent-4-enyl-cyclopentanone 2.29.

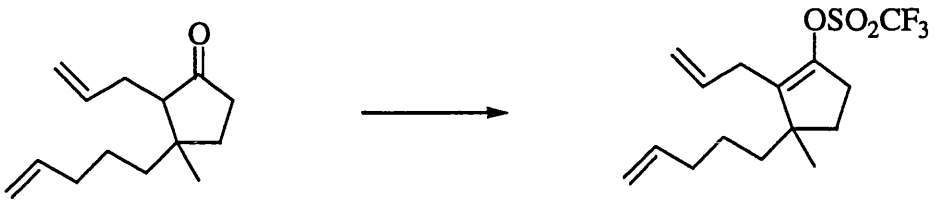


2.4 **2.29**

MeLi (5.40 mL of a 1.40 M solution in Et_2O, 7.56 mmol) was added dropwise to a stirred suspension of CuI (1.44 g, 7.56 mmol) in Et_2O (40 mL) under nitrogen at -40 °C. After stirring at this temperature for 5 min, the yellow slurry was cooled to -78 °C and $BF_3.Et_2O$ (1.11 g, 7.80 mmol) was added via a glass syringe. The thick, deep-yellow slurry was stirred for a further 5 min before the dropwise addition of a solution of pre-dried (over 4Å molecular sieve pellets) enone **2.4** (0.48 g, 2.52 mmol) in Et_2O (5 mL). The mixture was stirred at -78 °C for 5 h, quenched with saturated

NH_4Cl solution (30 mL), the phases separated and the aqueous re-extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4), solvent evaporated under reduced pressure and the residue chromatographed (SiO_2, light petroleum-Et_2O, 94:6) yielding a yellow oil (50 %) as a mixture of isomers (de 31% by ^1H NMR); R_f (light petroleum-Et_2O, 90:10): 0.40; $\nu_{max}(CDCl_3)/cm^{-1}$: 3076 (=CH), 2932 (CH), 1739 (C=O), 1640 (C=C); δ_H (270 MHz, $CDCl_3$): 0.83 (3H, s, Me, major isomer - 65.5 %), 1.12 (3H, s, Me, minor isomer - 34.5 %), 1.25-1.56 (4H, m), 1.59-1.75 (2H, m), 1.94-2.10 (5H, m), 2.14-2.33 (1H, m), 2.35-2.41 (1H, m), 4.95-5.09 (4H, m, H_2C=), 5.72-5.99 (2H, m, H_2C=C*H*CH_2); δ_C (270 MHz, $CDCl_3$): (major isomer) 19.7 (CH_3), 23.3 (CH_2), 29.2 (CH_2), 32.6 (CH_2), 34.2 (CH_2), 34.7 (CH_2), 40.9 (CH_2), 42.3 (Cq), 58.9 (CH), 114.6 (=CH_2), 115.4 (=CH_2), 137.4 (=CH), 138.7 (=CH), 219.6 (Cq), (minor isomer) 23.5 (CH_2), 26.2 (CH_3), 28.9 (CH_2), 31.5 (CH_2), 33.3 (CH_2), 34.3 (CH_2), 34.8 (CH_2), 42.0 (quaternary), 61.1 (CH), 114.7 (=CH_2), 115.5 (=CH_2), 137.3 (=CH), 138.4 (=CH); *m/z* (EI^+): 206 (11 %, M^+), 191 (6, M^+ - Me), 137 (47, M^+ - pentenyl), 96 (100), ($C_{14}H_{22}O$ requires *M*, 206.1671. Found: M^+, 206.1667).

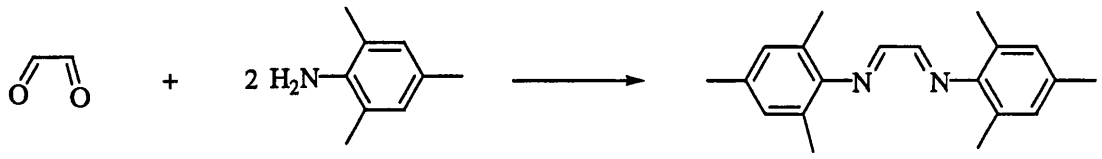
Preparation of 3-Methyl-3-(4-pentenyl)-2-allyl-1-cyclopen-1-yl trifluoromethanesulfonate 2.30.



2.29 **2.30**

KHMDS (1.6 mL of a 0.5 M solution in hexane, 0.8 mmol) was added to a cold (0 °C) solution of ketone **2.29** (170 mg, mmol) in THF (5 mL). The reaction mixture was then allowed to warm up to room temperature and was stirred for 12h. 2-[*N,N-bis*(trifluoromethylsulfonyl)amino]-5-chloropyridine (355 mg, 0.9 mmol) in THF (2 mL) was subsequently added and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was pre-adsorbed on silica and chromatographed (0.5 % of Et_3N in light petroleum) to yield 277 mg, 60 % of *vinyl triflate* **2.30** as a colourless oil. R_f (light petroleum): 0.28, $\nu_{max}(CDCl_3)/cm^{-1}$: 3079 (=CH), 2932 (C-H), 1419 and 1212 (-SO_2-O-); δ_H (400 MHz, $CDCl_3$): 1.07 (3H, s, CH_3), 1.30-1.44 (4H, m), 1.64.1.94 (2H, m), 1.98-2.06 (2H, m), 2.53-2.59 (2H, m, H_2C=CH-CH_2-CH_2), 2.71-2.91 (2H, m, CH_2=CH-CH_2-C=C(OTf)), 4.92-5.66 (4H, m, 2 × H_2C=CH), 5.68-5.84 (2H, m, 2 × H_2C=C*H*); δ_C (400 MHz, $CDCl_3$): 23.97 (CH_3), 26.89 (CH_2), 28.95 (CH_2), 29.38 (CH_2), 33.78 (CH_2), 34.53 (CH_2), 47.17 (Cq), 114.91 (=CH_2), 116.94 (Cq), 117.00 (=CH_2), 134.39 (=CH), 135.87 (Cq), 138.73 (=CH), 143.38 (Cq). δ_F (400 MHz, $CDCl_3$): -74.94.

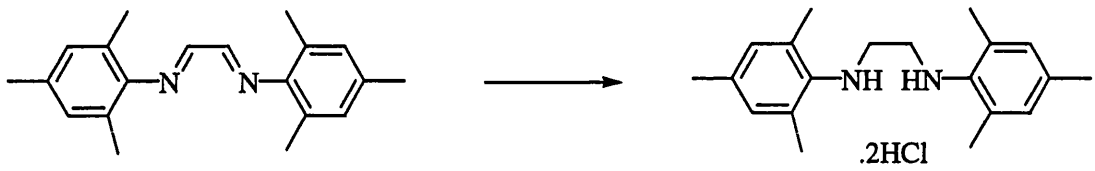
Preparation of Glyoxal-*bis*-(2,4,6-trimethylphenyl)imine 2.18 [4]



2.16 **2.17** **2.18**

Diimine **2.18** was synthesised following the procedure describe by Arduengo *et al* [4]. All analytical data matched with literature. We obtained 55 % yield on 40 g scale (of starting material glyoxal), Mp: 157-158 °C, bright yellow solid. δ_H (400 MHz, $CDCl_3$): 2.16 (12H, s, 4 × CH_3 *ortho*), 2.29 (6H, s, 2 × CH_3 *para*), 6.91 (4H, s, 4 × CH_{Ar}), 8.10 (2H, s, 2 × HCN); δ_C (100 MHz, $CDCl_3$): 18.33 (4 × *ortho*-CH_3Ar), 20.88 (2 × *para*-CH_3Ar), 126.42 (4 × *ortho*-Cq), 128.84 (4 × *meta*-CH_{Ar}), 134.11 (2 × *para*-Cq), 147.24 (2 × *ipso*-Cq), 163.27 (2 × C=N) *m/z* (EI^+): 293.0 (35 %, $[M-H]^+$); (Found: C, 82.30; H, 8.25; N, 9.97.$C_{20}H_{24}N_2$ requires C, 82.15, H, 8.27; N, 9.62).

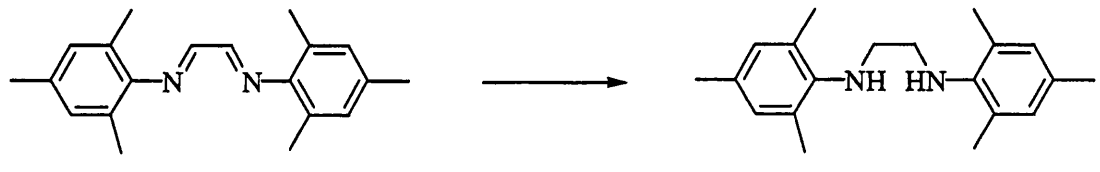
Preparation of *N,N'-Bis*-(2,4,6-trimethylphenylamino)ethane dihydrochloride 2.19 [4].



2.18 **2.19**

The procedure followed was first described by Arduengo *et al* [4]. All analytical data favourably compared with previous literature report. Yield: 85 % on a 30 g scale. Mp > 250 °C, colourless solid; δ_H (400 MHz, d^6-DMSO): 2.21 (6H, s, 2 × CH_3 *para*), 2.43 (12H, s, 4 × CH_3 *ortho*), 3.66 (4H, s, 2 × CH_2), 4.19 (2H, bs, 2 × NH), 6.69 (4H, s, 4 × CH); δ_C (100 MHz, d^6-DMSO); 18.17 (4 × *ortho*-CH_3), 20.36 (2 × *para*-CH_3), 46.08 (2 × NCH_2), 130.15 (2 × *ipso*-Cq), 131.41 (4 × *meta*-CH_{Ar}), 132.65 (4 × *ortho*-C), 137.09 (2 × *para*-Cq), *m/z* (EI^+): 296.1 (15 %, M^+), (Found: C, 64.40; H, 8.11, N, 7.41. $C_{20}H_{30}N_2Cl_2$ requires C, 65.02, H, 8.11, N, 7.58).

Preparation of *N,N'-Bis*-(2,4,6-trimethylphenylamino)ethane 2.20 [5].

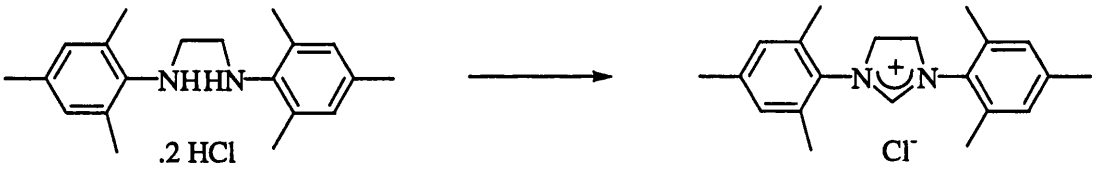


2.18 **2.20**

Bis-imine **2.18** (5.00 g, 0.017 mol) was suspended in 30 mL of MeOH and the mixture was cooled to 0 °C. $NaBH_4$ (0.98 g, 0.026 mol) was introduced portionwise

over 15 min. The reaction mixture was then stirred for a further 2 hours, and quenched with 6 M HCl (20 mL). The mixture was warmed to room temperature, stirred for 1 h before a saturated solution of Na_2CO_3 was introduced until pH remained weakly alkaline (pH = 8 – 9). Water (50 mL) was added and the resulting mixture was extracted with Et_2O (3 × 30 mL), dried over $MgSO_4$, concentrated *in vacuo* to yield (3.62 g, 72 %) as a clear oil. Analytical data matched with earlier reports [5]. δ_H (400 MHz, $CDCl_3$): 2.22 (6H, s, 2 × CH_3 *para*), 2.28 (12H, s, 4 × CH_3 *ortho*), 3.13 (4H, s, 2 × CH_2), 3.17 (2H, bs, 2 × NH), 6.81 (4H, s, 4 × CH_{Ar}), δ_C (100 MHz, $CDCl_3$): 19.00 (4 × *ortho*-CH_3), 21.13 (2 × CH_3), 49.64 (2 × CH_2), 129.82 (2 × *ipso*-Cq), 130.07 (4 × *meta*-CH_{Ar}), 131.75 (2 × *ortho*-Cq), 143.66 (2 × *para*-Cq).

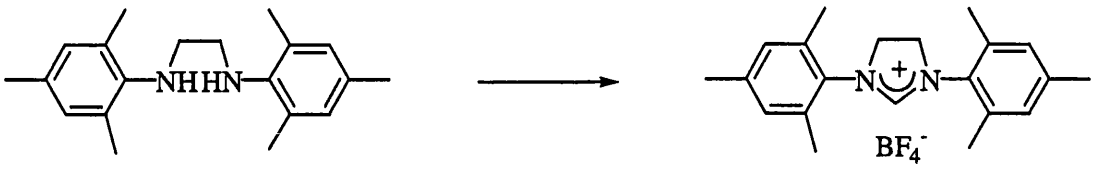
Preparation of 1,3-*Bis*-(2,4,6-trimethylphenyl)imidazolinium chloride 2.22 [4].



2.19 **2.22**

Imidazolium salt **2.22** was synthesised according to literature [4]. Yield: 86 % on a 10 g scale. Mp > 250 °C, colourless solid; δ_H (400 MHz, d^6-DMSO): 2.29 (6H, s, 2 × CH_3 *para*), 2.35 (12H, s, 4 × CH_3 *ortho*), 4.46 (4H, s, 2 × CH_2), 7.09 (4H, s, 4 × CH_{Ar}, *meta*), 9.11 (1H, s, CH), δ_C (100 MHz, d^6-DMSO): 17.23 (4 × *ortho*-CH_3), 20.57 (2 × *para*-CH_3), 50.89 (2 × CH_2), 129.32 (4 × CH_{Ar}), 130.66 (2 × *ipso*-Cq), 135.14 (4 × *ortho*-Cq), 139.37 (2 × *para*-Cq), 159.97 (CH), *m/z* (FAB$^+$): 307.1 (100 %, M^+ cation).

Preparation of 1,3-*Bis*-(2,4,6-trimethylphenyl)imidazolinium tetrafluoroborate 2.21 [5].

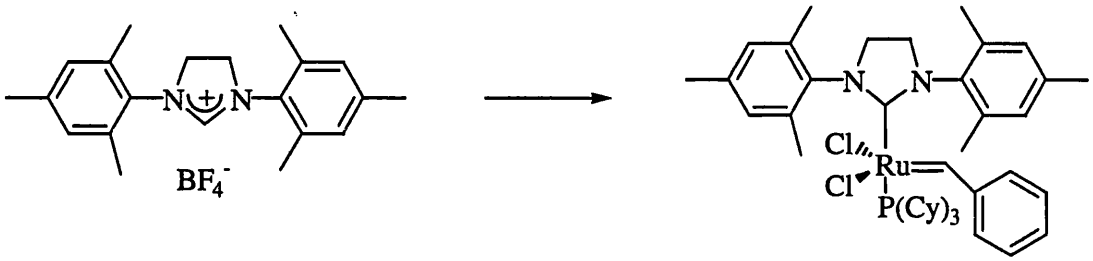


2.20 **2.21**

Imidazolium salt **2.21** was synthesised according to literature [5].

Yield: 82 % on a 0.5 g scale. Mp > 250 °C, colourless solid; δ_H (400 MHz, d^6-DMSO): 2.27 (6H, s, 2 × CH_3 *para*), 2.33 (12H, s, 4 × CH_3 *ortho*), 4.42 (4H, s, 2 × CH_2), 7.07 (4H, s, 4 × CH_{Ar}), 8.96 (1H, s, MsNCHNMs), δ_C (100 MHz, d^6-DMSO): 18.07 (4 × *ortho*-CH_3), 21.45 (2 × *para*-CH_3), 51.67 (2 × CH_2), 130.09 (4 × *meta*-CH_{Ar}), 131.52 (2 × *ipso*-Cq), 136.03 (4 × *ortho*-Cq), 140.28 (2 × *para*-Cq), 160.85 (CH); *m/z* (FAB^+): 307.1 (100 %, M^+ cation). (Found: C, 63.70; H, 6.95; N, 6.99. $C_{21}H_{27}BF_4N_2$ requires C, 63.97; H, 6.90; N, 7.11).

Preparation of Tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazole-2-ylidene][benzylidine]ruthenium(IV)dichloride 2.15 [5 6].

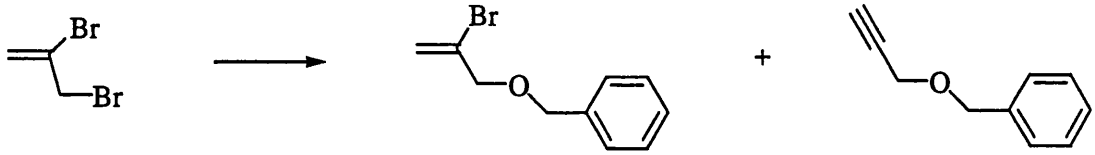


2.21 **2.15**

Ruthenium catalyst **2.15** was synthesised according to former literature reports [6 5]. The following spectroscopic data is in accordance: δ_P (121 MHz, $CDCl_3$): 30.27 ($P(Cy)_3$); *m/z* (FAB^+): 848.2 (30 %; M^+); (Found: C, 64.80; H, 7.57; N, 3.34.$C_{46}H_{65}N_2PCl_2Ru$ requires C, 65.08; H, 7.71; N, 3.30).

4.3 Chapter 3 experimental

Preparation of (2-Bromo-allyloxymethyl)-benzene 3.11 and prop-2-ynyloxymethyl-benzene 3.12



3.10 **3.11** **3.12**

Typical procedure: Benzyl alcohol (1.08 g, 0.01 mol) and sodium *t*-butoxide (0.96 g, 0.01 mol) were stirred in THF (50 mL) at 0 °C for one hour. 2,3-dibromo-propene **3.10** (2.00 g, 0.01 mmol) was then introduced dropwise *via* a glass syringe. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was then quenched with brine (30 mL), the ethereal layer separated and the aqueous layer extracted with Et_2O (3 × 10 mL). The organic extrats were combined, washed with brine (3 × 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (SiO_2, light-petroleum-Et_2O, 99:1) to afford *alkene* **3.11** (1.22 g, 54 %) as a pale yellow oil: R_f (light petroleum-Et_2O, 95:5): 0.60, bp 117-119 °C at 1 mm Hg, $\nu_{max}(CHCl_3)/cm^{-1}$: 3019 (C-H), 2853 (C-H), 1632 (C=C), 1491 (C=C), 1447 (C=C), 1082 (C-O-C), δ_H (400 MHz, $CDCl_3$): 4.09-4.10 (2H, m, $CBrCH_2O$), 4.52 (2H, s, OCH_2Ph), 5.61-5.62 (1H, m, $CBrCH_AH_B$), 5.91-5.93 (1H, m, $CBrCH_AH_B$), 7.26-7.34 (5H, m, CH_{Ar}), δ_C (100 MHz, $CDCl_3$): 72.46 (CH_2), 74.38 (CH_2), 118.24 (CH_2), 128.23 (CH_{Ar}), 128.29 (CH_{Ar}), 128.89 (CH_{Ar}), 129.86 (Cq), 137.92 (Cq), *m/z* (EI^+):

227. 9 (10 %, [^{81}Br] M^+), 225.9 (10 %, [^{79}Br] M^+), 227 91.1 (100%, benzyl cation), ($C_{10}H_{11}O$ requires *M*, 225.9993. Found M^+ 225.9974), and (0.20 g, 18 %) of alkyne **3.12** as a clear oil: R_f (light petroleum-Et_2O, 95:5): 0.47, bp 110-112 °C at 11.5 mm Hg, $\nu_{max}(CHCl_3)/cm^{-1}$: 3291 (C-H), 3031 (C-H), 2855 (C-H), 2116 (C≡C), 1496 (C=C), 1454 (C=C), 1075 (C-O-C), δ_H (400 MHz, $CDCl_3$): 2.47 (1H, t, *J* 2.4, CH_2CCH), 4.18 (2H, d, *J* 2.4, CCH_2O), 4.62 (2H, s, CH_2Ph), 7.31-7.38 (5H, m, CH_{Ar}), δ_C (100 MHz, $CDCl_3$): 56.92 (CH_2), 71.35 (CH_2), 74.53 (Cq), 79.58 (CH), 127.76 (CH_{Ar}), 127.97 (CH_{Ar}), 128.31 (CH_{Ar}), 137.20 (Cq_{Ar}), *m/z* (EI^+): 145.1 (15 %, M^+), 91.1 (100 %, benzyl cation), ($C_9H_{10}O$ requires *M*, 145.0653. Found M^+ 145.0652).

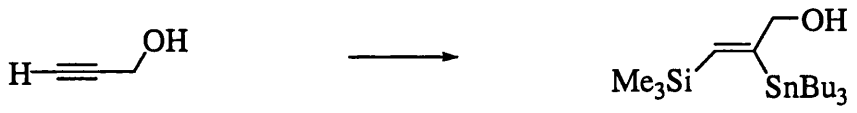
Preparation of (1-Benzyloxymethyl-vinyl)-tri-n-butylstannane 3.14.

3.12 **3.14**

Under an inert atmosphere of nitrogen, *tris*(dibenzylideneacetone)dipalladium(0) (26 mg, 0.028 mmol) and triphenylphosphine (16 mg, 0.056 mmol) were stirred together in THF (1 mL) until the solution became clear. Alkyne **3.12** (91 mg, 0.62 mmol) and (trimethylsilyl)tributylstannane (0.23 g, 0.71 mmol) were subsequently introduced and the reaction mixture was heated at reflux for four hours. A solution of *tetra-n*-butylammonium fluoride (TBAF) (1.86 mL of 1.0 M solution in THF, 1.86 mmol) was slowly added and the reflux was maintained for a further 12 hours. The resulting solution was cooled to room temperature, quenched with water (2 mL) and diluted with Et_2O (3 mL). The organics were separated, the aqueous re-extracted with Et_2O

(2 × 1 mL) and the combined ethereal layers were washed with brine (3 ×1 mL), dried over $MgSO_4$ and concentrated. The crude mixture was chromatographed (SiO_2, light petroleum-Et_2O, 99:1) to provide *stannane* **3.14** as a colourless oil (0.176 g, 65 %): R_f (light petroleum): 0.28, $\nu_{max}(CHCl_3)/cm^{-1}$: 3030 (C-H), 2961 (C-H), 2860 (C-H) 1698 (C=C), 1653 (C=C), 1450 (C=C), 1089 (C-O-C), δ_H (400 MHz, $CDCl_3$): 0.85-0.92 (15H, m, 3 × [Sn($CH_2C_3H_7$)] and 3 × [$SnC_3H_6CH_3$]), 1.24-1.33 (6H, m, 3 × [$SnCH_2CH_2C_2H_5$]), 1.40-1.53 (6H, m, 3 × [$SnC_2H_4CH_2CH_3$]), 4.11-4.19 (2H, m, $BnOCH_2$), 4.49 (2H, s, OCH_2Ph), 5.23-5.29 (1H, m, H_aH_bC=C), 5.87-5.89 (1H, m, H_aH_bC=C), 7.27-7.36 (5H, m, CH_{Ar}), δ_C (100 MHz, $CDCl_3$): 9.54 ($SnCH_2C_3H_7$), 13.67 (CH_3), 27.31 ($SnCH_2CH_2C_2H_5$), 29.03 ($SnC_2H_4CH_2CH_3$), 71.95 (CH_2), 77.20 (CH_2), 124.48 (CH_{Ar}), 127.12 (CH_{Ar}), 127.38 (CH_{Ar}), 127.95 (CH_{Ar}), 138.18 (CqAr), 152.51 (Cq), *m/z* (FAB^+): 381.0 (100 %, M^+-Bu)

Preparation of 2-Tributylstannyl-3-trimethylsilanyl-prop-2-en-1-ol 3.15



3.15

Under an inert atmosphere of nitrogen, tris(dibenzylideneacetone)dipalladium(0) (63 mg, 0.138 mmol) and triphenylphosphine (80 mg, 0.28 mmol) were stirred together in THF (2 mL) until the solution became clear. Propargyl alcohol (0.14 g, 2.51 mmol) and (trimethylsilyl)tri-n-butylstannane (1.00 g, 2.76 mmol) were subsequently introduced and the reaction mixture was heated at reflux for four hours. The resulting solution was cooled to room temperature, quenched with water (2 mL) and diluted with Et_2O (3 mL). The organics were separated, the aqueous re-extracted with Et_2O

(3 × 2 mL) and the combined ethereal layers were washed with brine (2 × 5 mL), dried over $MgSO_4$ and concentrated. The crude mixture was chromatographed (SiO_2, light petroleum-Et_2O, 99:1) to provide silyl stannane **3.15** as a pale yellow oil (0.71 g, 68 %): R_f (light petroleum): 0.29, $\nu_{max}(CHCl_3)/cm^{-1}$: 3336 (O-H), 2950 (C-H), 2920 (C-H) 2849 (C-H), δ_H (400 MHz, $CDCl_3$): 0.12 (9H, s, 3 × CH_3Si), 0.89 (9H, t, *J* 7.2, 3 × [$SnC_3H_6CH_3$]), 0.95-1.01 (6H, m, 3 × [$Sn(CH_2C_3H_7]$) 1.24-1.36 (6H, m, 3 × [$SnCH_2CH_2C_2H_5$]), 1.41-1.54 (6H, m, 3 × [$SnC_2H_4CH_2CH_3$]), 4.23 (2H, d, *J* 3.6, CH_2OH), 6.61 (1H, m, *H*C=C), δ_C (100 MHz, $CDCl_3$): 0.18 ($SiCH_3$) 10.92 ($SnCH_2C_3H_7$), 13.65 ($SnC_3H_6CH_3$), 27.40 ($SnCH_2CH_2C_2H_5$), 29.14 ($SnC_2H_4CH_2CH_3$), 73.40 (CH_2OH), 140.08 (*C*H=Cq), 163.15 (CH=*C*q), *m/z* (FAB^+): 363.0 (100 %, M^+-Bu).

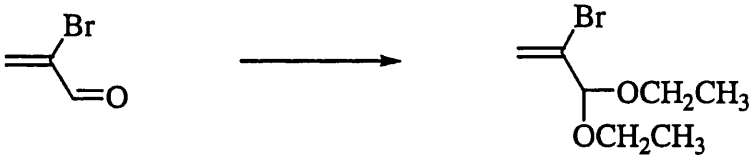
Preparation of 2-Bromo-propenal (2-bromoacrolein) 3.18.

3.18

Acrolein (1.00 g, 17.80 mmol) was stirred in dry dichloromethane (30 mL) at 0 °C in a two-neck flask equipped with a droping funnel. A solution of bromine (3.00 g, 18.77 mmol) in dry dichloromethane (5 mL) was added dropwise *via* the droping funnel to the reaction mixture until a brown colour persisted. Freshly distilled triethylamine (6.10 g, 59.30 mmol) was then introduced with a glass syringe and the reaction was slowly allowed to warm up to room temperature. After two hours, the reaction was quenched with brine (25 mL). The organic phase was separated from the aqueous layer, which was re-extracted with dichloromethane (3 × 10 mL). The

combined organics were then washed with 20 mL of a 10 % solution of sodium thiosulphate, 20 mL of 0.1 M solution of HCl, distilled water (20 mL) and brine (20 mL). After drying over $MgSO_4$, the solvent was carefully evaporated to yield 2-bromoacrolein **3.18** (1.44 g, 60 %) as a brown oil. Spectroscopic data were in accordance with literature [7]. R_f (light petroleum-Et_2O, 95:5): 0.27, $\nu_{max}(CHCl_3)/cm^{-1}$: 3107 (C-H), 2989 (C-H), 2842 (C-H), 1700 (C=O), 1598 (C=C), δ_H (400 MHz, $CDCl_3$): 6.92 (2H, s, CH_2), 9.27 (1H, s, CH), δ_C (100 MHz, $CDCl_3$): 132.28 (CH), 136.61 (CH_2), 185.46 (C=O).

Preparation of 2-Bromo-3,3-diethoxy-propene 3.19 [7].



3.19

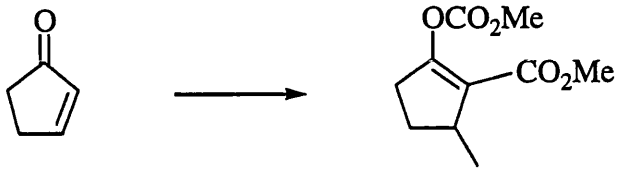
The procedure was followed as described by [7]. Analytical data were in accordance with literature. R_f (light petroleum-Et_2O, 95:5): 0.56, bp 83-85 °C at 6 mm Hg, ν_{max} $(CHCl_3)/cm^{-1}$: 2972 (C-H), 2888 (C-H), 1620 (C=C), 1065 (C-O-C), δ_H (400 MHz, $CDCl_3$): 1.25 (6H, t, *J* 7, 2 × OCH_2CH_3), 3.50-3.57 (2H, m, OCH_AH_BCH3), 3.60-3.68 (2H, m, $OCH_AH_BCH_3$), 4.83 (1H, bs, $CH(OCH_2CH_3)_2$), 5.73 (1H, m, $C{=}CH_CH_D$), 6.12-6.13 (1H, m, $C{=}CH_DH_C$), δ_C (100 MHz, $CDCl_3$): 15.14 (CH_3), 61.76 (CH_2), 101.44 (CH), 119.31 (CH_2=Cq), 129.80 (Cq=CH_2).

Preparation of 2-(1-Bromo-vinyl)-[1,3]dioxolane 3.20.

3.19 **3.20**

Acyclic acetal **3.19** (0.40 g, 1.91 mmol), diethylene glycol (0.82 g, 10.80 mmol) and cerium trichloride heptahydrate (0.07 g, 0.19 mmol) were heated at reflux overnight in tetrahydrofuran (2 mL). The reaction mixture was allowed to cool down to room temperature and distilled water (5 mL) was introduced. The ethereal layer was separated and the aqueous layer was extracted with diethyl ether (3 × 7 mL). The combined organics were then washed with distilled water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude mixture was chomatographed (SiO_2, light petroleum-Et_2O, 98:2), to yield *cyclic acetal* **3.20** (0.18 g, 52 %) as a colourless oil. R_f (light petroleum-Et_2O, 98:2): 0.31, $\nu_{max}(CHCl_3)/cm^{-1}$: 2977 (C-H), 2850 (C-H), 1632 (C=C), δ_H (400 MHz, $CDCl_3$): 3.97-4.03 (2H, m, OCH_2CH_2O), 4.10-4.13 (2H, m, OCH_2CH_2O), 5.33 (1H, s, CH), 5.74 (1H, d, *J* 2.2, $CBrCH_AH_B$), 6.10 (1H, dd, *J* 0.8 and 2.2, $CBrCH_AH_B$), δ_C (100 MHz, $CDCl_3$): 65.91 (2 × OCH_2), 103.27 (CH), 120.78 ($C=CH_2$), 131.12 (Cq).

Preparation of 2-Methoxycarbonyloxy-5-methyl-cyclopent-1-enecarboxylic acid methyl ester 3.21.

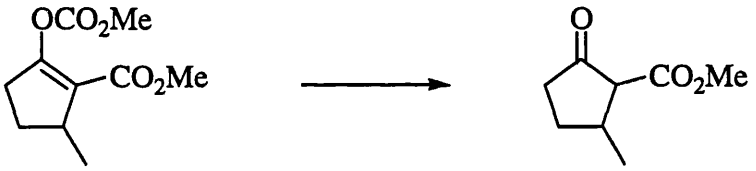


3.21

In a flame dried two-neck flask a suspension of copper(I) iodide (15.20 g, 0.08 mol) in dry Et_2O (200 mL) was cooled down to –78 °C under an inert atmosphere of nitrogen. Methyl lithium (100 mL of a 1.6 M solution in Et_2O, 160 mmol) was then added drop wise with a glass syringe. Once the addition had been completed, the reaction mixture was warmed up to –40 °C for 30 minutes; the resulting clear homogeneous solution was cooled down to –78 °C. A solution of cyclopentenone (6.75 g, 0.08 mol) in dry Et_2O (50 mL) was slowly added over 5 minutes *via* a cannula; a grey precipitate formed instantaneously. After an hour at –78 °C, methylchloroformate (45.36 g, 0.48 mol) was introduced with a glass syringe. The reaction mixture was slowly allowed to warm up to room temperature and was stirred overnight. A solution of saturated ammonium chloride (300 mL) was then introduced. The resulting solution was filtered, the organics separated, and the aqueous extracted with Et_2O (3 × 75 mL). The combined organics were washed with distilled water (3 × 100 mL), brine (2 × 100 mL) and dried over $MgSO_4$. The crude mixture was concentrated *in vacuo*, purified by flash column chromatography (SiO_2, light petroleum-Et_2O, 97:3) to yield *enol ester carbonate* **3.21** (7.6 g, 45 %) as a colourless oil. R_f (light petroleum-Et_2O, 85:15): 0.17, $\nu_{max}(CHCl_3)/cm^{-1}$: 2953 (C-H),

1768 (C=O), 1709 (C=O), 1658 (C=C), 1291 (C-O), 1206 (C-O); δ_H (400 MHz, $CDCl_3$): 1.12 (3H, d, *J* 6.8, $CHCH_3$), 1.44-1.51 (1H, m, $CH_AH_BCHCH_3$), 2.08-2.18 (1H, m, $CH_AH_BCHCH_3$), 2.45-2.53 (1H, m, $CH_CH_DC(OCO_2CH_3)$), 2.63-2.73 (1H, m, $CH_DH_CC(OCO_2CH_3)$), 2.96-3.03 (1H, m, $CHCH_3$), 3.66 (3H, s, CO_2CH_3), 3.81 (3H, s, OCO_2CH_3); δ_C (100 MHz, $CDCl_3$): 20.52 (CH_3CH), 28.46 (CH_2), 31.75 (CH_2), 37.28 (CH), 51.54 (CO_2CH_3), 55.80 (OCO_2CH_3), 122.78 (Cq), 152.07 (Cq), 158.77 (Cq), 163.91 (Cq); *m/z* (EI^+): 214.1 (30 %, M^+), 155.1 (100 %, M^+-CO_2CH_3), ($C_{10}H_{14}O_5$ requires *M*, 214.0841. Found M^+, 214.0838).

Preparation of 2-Methyl-5-oxo-cyclopentanecarboxylic acid methyl ester 3.22.

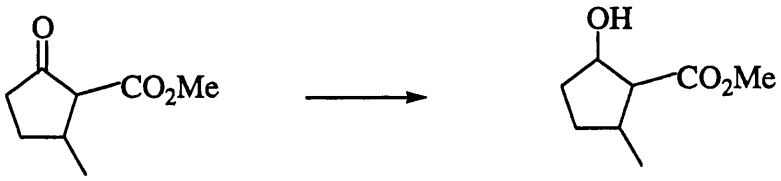


3.21 **3.22**

Enol carbonate **3.21** (0.60 g, 2.8 mmol) was stirred at room temperature for 2 hours with 10 mL of methanol and 2.2 mL of a 1.5 M (3.30 mmol) solution of sodium methoxide in methanol. Most of the methanol was then removed under vacuum. Dichloromethane (25 mL) was added to the residue together with 25 mL of saturated ammonium chloride. The organic layer was separated and the aqueous re-extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine (3 × 15 mL) and dried over $MgSO_4$. Evaporation of the solvent provided *keto ester* **3.22** as a pale yellow oil (0.42 g, 95 %). R_f (light petroleum-Et_2O, 75:25): 0.20, $\nu_{max}(CHCl_3)/cm^{-1}$: 2954 (C-H), 1754 (C=O), 1726 (C=O ester); δ_H (400 MHz, $CDCl_3$): 1.19 (3H, d, *J* 6.0, $CHCH_3$), 1.44-1.55 (1H, m, $CH_ACH_BCH_2CO$), 2.18-2.28

(1H, m, $CH_ACH_BCH_2CO$), 2.30-2.48 (2H, m, CH_2CO), 2.58-2.63 (1H, m, $CHCH_3$), 2.79 (1H, d, *J* 11.2, $CHCO_2CH_3$), 3.76 (3H, s, CO_2CH_3); δ_C (100 MHz, $CDCl_3$): 19.29 ($CHCH_3$), 29.33 (CH_2), 36.36 ($CHCH_3$), 38.74 (CH_2), 52.34 (CO_2CH_3), 62.87 ($CHCO_2CH_3$), 169.3 (CO_2CH_3), 211.49 (C=O); *m/z* (EI^+): 156.1 (15 %, M^+), 141.1 (20 %, M^+-CH_3), 128.1 (55 %, M^+-CO), ($C_8H_{12}O_3$ requires *M*, 156.0786. Found M^+, 156.0783).

Preparation of 2-Hydroxy-5-methyl-cyclopentanecarboxylic acid methyl ester 3.32.

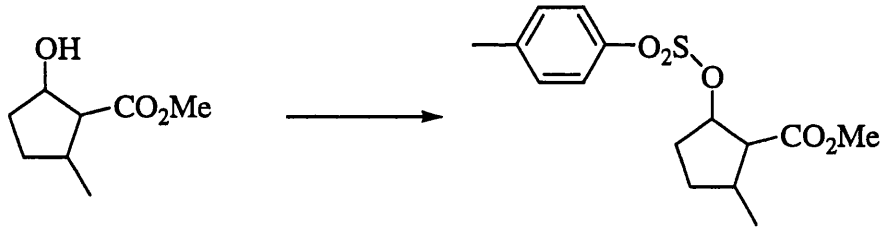


3.22 **3.32**

A solution of keto ester **3.22** (0.70 g, 4.45 mmol) in methanol (23 mL) was stirred at 0 °C under an inert atmosphere of nitrogen. Sodium borohydride (0.132g, 2.96 mmol) was added portionwise and the mixture was stirred for an additional hour at 0 °C. The reaction was then quenched by the slow addition of 20 mL of brine, the mixture was extracted with Et_2O (3 × 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (SiO_2, light petroleum-ethyl acetate, 90:10) to afford *hydroxy ester* **3.32** (0.48 g, 70 %) as a colourless oil and a mixture of two separable sets of diastereoisomers. R_f (light petroleum-ethyl acetate, 85:15): 0.20 (minor set of isomers), 0.22 (major set of isomers) $\nu_{max}(CHCl_3)/cm^{-1}$: 3472 (O-H), 2956 (C-H), 1734 (C=O), δ_H (400 MHz, $CDCl_3$): minor set of diatereoisomers: 1.10 (3H, d, *J* 6.4, $CHCH_3$), 1.17-1.20 (1H, m, $CH_AH_BCHCH_3$), 1.69-1.77 (1H, m, $CH_AH_BCHCH_3$), 1.90-1.97 (1H, m,

CH_CH_DCHOH), 2.11-2.21 (1H,m, CH_DH_CCHOH), 2.26 (1H, dd, *J* 10.0 and 4.6, $CHCO_2CH_3$), 2.41-2.53 (1H, m, $CHCH_3$), 3.12 (1H, bs, OH), 3.74 (3H, s, CO_2CH_3), 4.44 (1H, bs, CHOH), major set of diastereoisomers: 1.11 (3H, d, *J* 6.4, $CHCH_3$), 1.39-1.49 (1H, m, $CH_AH_BCHCH_3$), 1.63-1.71 (1H, m, $CH_AH_BCHCH_3$), 1.82-1.90 (1H, m, CH_CH_DCHOH), 1.96-2.05 (1H, m, CH_DH_CCHOH), 2.11-2.21 (1H, m, $CHCH_3$), 2.26 (1H, dd, *J* 10.0 and 7.0, $CHCO_2CH_3$), 3.73 (3H, s, CO_2CH_3), 4.37-4.42 (1H, m, CHOH), δ_C (100 MHz, $CDCl_3$): minor set of diastereoisomers: 20.29 ($CHCH_3$), 31.29 (CH_2), 33.44 (CH_2), 36.88 ($CHCH_3$), 51.81 ($CHCO_2CH_3$), 60.66 (CO_2CH_3), 76.55 (CHOH), 174.99 (C=O), major set of diastereoisomers: 20.02 ($CHCH_3$), 31.56 (CH_2), 33.76 (CH_2), 35.58 ($CHCH_3$), 51.77 ($CHCO_2CH_3$), 56.99 (CO_2CH_3), 74.5 (CHOH), 174.90 (CO), *m/z* (CI^+): 159.1 (50 %, $[M-H]^+$).

Preparation of 2-Methyl-5-(toluene-4-sulfonyloxy)cyclopentanecarboxylic acid methyl ester 3.33.

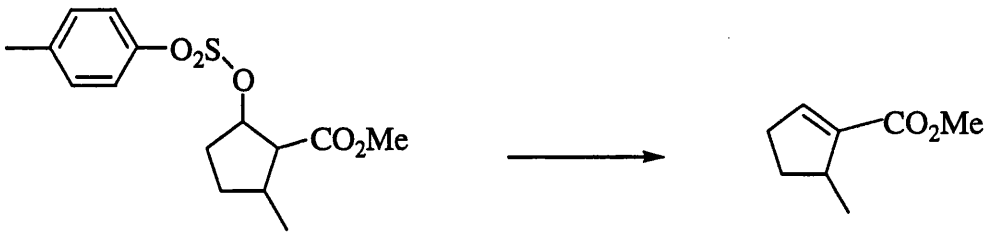


3.32 **3.33**

Hydroxy ester **3.32** (0.60 g, 3.70 mmol) was stirred in 22 mL of dry pyridine under an inert atmosphere of nitrogen. *p*-Toluenesulphonyl chloride (0.81 g, 4.25 mmol) was introduced and the reaction mixture was stirred for 3 days at room temperature. The reaction was then quenched with saturated ammonium chloride (25 mL) and was extracted with Et_2O (3 × 20 mL). The organics were combined, washed with water (20 mL), brine (20 mL) and dried over $MgSO_4$. The solvent was evaporated and the

crude mixture chromatographed (SiO_2, light petroleum-ethyl acetate, 90:10) to afford the *tosylate ester* **3.33** (0.76 g, 60 %) as a colourless oil. In the ^1H NMR spectrum, the AA'BB' system resulting from the aromatic protons resonance was approximated to an AB system. R_f (light petroleum-ethyl acetate, 80:20): 0.48, ν_{max} ($CHCl_3$)/cm^{-1}: 2953 (C-H), 1735 (C=O), 1588 (C=C), 1359 (S=O), 1147 (S=O), δ_H (400 MHz, $CDCl_3$): minor set of diastereoisomers: 1.04 (3H, d, *J* 6.8, $CHCH_3$), 1.15-1.24 (1H, m, $CHCH_3$), 1.92-2.11 (3H, m, 5-membered ring protons), 2.40 (1H, dd, *J* 10.8 and 5.6, $CHCO_2CH_3$), 2.44 (3H, s, Ar-CH_3), 2.49-2.57 (1H, m, 5-membered ring proton), 3.50 (3H, s, CO_2CH_3), 5.19 (1H, ddd, *J* 5.2, 4.6 and 2.8, CHOTs), 7.33 (2H, d, *J* 8.4, CH_{Ar}), 7.75 (2H, d, *J* 6.4, CH_{Ar}) major set of diastereoisomers: 1.11 (3H, d, *J* 6.4, $CHCH_3$), 1.40-1.51 (1H, m, $CHCH_3$), 1.79-2.06 (4H, m, 5-membered ring protons), 2.45 (3H, s, Ar-CH_3), 2.52 (1H, dd, *J* 9.2 and 5.2, $CHCO_2CH_3$) 5.05-5.08 (1H, m, CHOTs), 7.30 (2H, d, *J* 8, CH_{Ar}), 7.77 (2H, d, *J* 6.8, 2 × CH_{Ar}), δ_C (100 MHz, $CDCl_3$): minor set of diastereoisomers: 19.62 (Ar-CH_3), 21.74 ($CHCH_3$), 30.91 (CH_2), 32.38 (CH_2), 33.92 ($CHCH_3$), 51.58/51.71 ($CHCO_2CH_3$), 57.01 (CO_2CH_3), 84.94 (CHOTs), 127.61 (CH_{Ar}), 129.53 (CH_{Ar}), 134.15 (C_{qAr}), 144.36 (C_{qAr}), 170.04 (C=O), major set of diastereoisomers: 19.55 (Ar-CH_3), 21.75 ($CHCH_3$), 32.53 (CH_2), 32.61 (CH_2), 39.05 ($CHCH_3$), 51.94 ($CHCO_2CH_3$), 58.51 (CO_2CH_3), 85.33 (CHOTs), 127.87 (CH_{Ar}), 129.62 (CH_{Ar}), 133.53 (Cq_{Ar}), 144.48 (Cq_{Ar}), 173.28 (C=O), *m/z* (EI^+), 312.1 (25 %, M^+), 91.0 (98 %, benzyl cation), ($C_{15}H_{20}O_5S$ requires *M*, 312.1031. Found M^+, 312.1018).

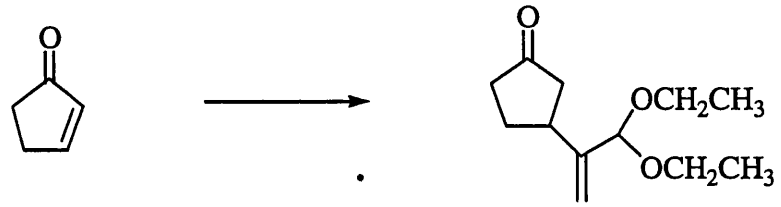
Preparation of 5-Methyl-cyclopent-1-enecarboxylic acid methyl ester 3.34.



3.33 **3.34**

Tosylate ester **3.33** (0.126 g, 0.4 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.091 g, 0.6mmol) were stirred in dry DMF (3 mL). The resulting solution was heated to 80 °C for 1.5 hour. The reaction was then cooled to room temperature and quenched with 10 mL of water and 10 mL of Et_2O. The organic layer was separated from the aqueous layer, which was re-extracted with Et_2O (3 × 5 mL). The combined organics were washed with a solution of saturated ammonium chloride (7 mL), distilled water (7 mL), brine (7 mL) and dried over $MgSO_4$. The solvent was evaporated to afford *unsaturated ester* **3.34** (0.042 g, 75 %) as a pale yellow oil. R_f (light petroleum-ethyl acetate, 90:10): 0.40, $\nu_{max}(CHCl_3)/cm^{-1}$: 3051 (C-H), 2942 (C-H), 1713 (C=O), 1621 (C=C), 1261 (C-O), δ_H (400 MHz, $CDCl_3$): 1.13 (3H, d, *J* 6.8, $CHCH_3$), 1.52-1.60 (1H, m, $CH_AH_BCHCH_3$), 2.13-2.24 (1H, m, $CH_AH_BCHCH_3$), 2.33-2.42 (1H, m, $CH_CH_DCHC(CO_2CH_3)$), 2.46-2.57 (1H, m, $CH_CH_DCH(CO_2CH_3)$), 2.95-3.04 (1H, m, $CHCH_3$), 3.73 (3H, s, CO_2CH_3), 6.72-6.74 (1H, m, $CHC(CO_2CH_3)$), δ_C (100 MHz, $CDCl_3$): 20.01 ($CHCH_3$), 31.48 (CH_2), 32.31 (CH_2), 38.87 ($CHCH_3$), 51.22 (CO_2CH_3), 140.84 (CH=Cq), 143.17 (Cq=CH), 165.49 (C=O).

Preparation of 3-(1-Diethoxymethyl-vinyl)-cyclopentanone 3.29.

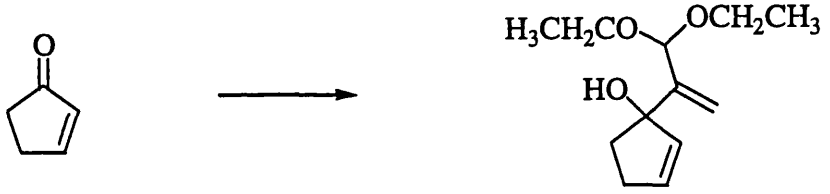


3.29

In a flame dried two-neck flask, a solution of **3.19** (0.40 g, 1.92mmol) in Et_2O (3 mL) was cooled to –78 °C under an inert atmosphere of nitrogen. *t*-Butyl-lithium (1.12 mL of a 1.7 M solution in pentane, 1.90 mmol) was introduced dropwise with a glass syringe and the reaction was stirred for 45 min at –78 °C. Lithiated alkene **3.19** was then transferred *via* a cannula to a solution of $[CuI.PBu_3]_4$ [2] (0.38 g, 0.24 mmol) in Et_2O (1 mL) at –78 °C. The resulting organocuprate (yellow homogeneous solution) was stirred at this temperature for an additional 30 min. A solution of cyclopentenone (0.08 g, 0.96 mmol) in Et_2O (1 mL) was then added *via* another cannula to the organocuprate solution: a yellow-grey precipitate formed immediately. After 1 hour at –78 °C the reaction mixture was quenched with a solution of saturated ammonium chloride (5 mL). The resulting solution was filtered, the organics separated and the aqueous extracted with Et_2O (3 × 5 mL). The combined organics were then washed with water (7 mL), brine (7 mL) and dried over $MgSO_4$. The solvent was evaporated and the crude mixture chromatographed (SiO_2; light petroleum-ethyl acetate, 95:5) to yield *ketone* **3.29** (0.135 g, 70 %) as a colourless oil. R_f (light petroleum-ethyl acetate, 90:10): 0.26, $\nu_{max}(CHCl_3)/cm^{-1}$: 2965 (C-H), 1736 (C=O), 1115 (C-O-C), δ_H (400 MHz, $CDCl_3$): 1.20 (3H, t, *J* 6.4, OCH_2CH_{3A}), 1.23 (3H, t, *J* 7, OCH_2CH_{3B}), 1.78-1.88 (1H, m, $CH_AH_BCH_2CO$), 2.10-2.32 (3H, m,

$CH_ACH_BCH_2CO$ and CH_2CH_2CO), 2.37 (1H, dd, *J* 17.4 and 8.2, $CHCH_CCH_DCO$), 2.50 (1H, dd, *J* 17.4 and 7.2, $CHCH_CCH_DCO$), 2.90-3.00 (1H, m, $CHCH_2CO$), 3.42-3.50 (2H, m, $OCH_{2E}CH_3$), 3.57-3.65 (2H, m, $OCH_{2F}CH_3$), 4.80 (1H, bs, $CHOCH_2CH_3$), 5.07 (1H, bs, $C=CH_GH_H$), 5.27 (1H, d, *J* 0.8, $C=CH_HH_G$), δ_C (100 MHz, $CDCl_3$): 15.25 (CH_3), 29.07 (CH_2), 37.71 ($CHCH_2CO$), 38.55 (CH_2), 44.83 (CH_2), 61.82 (OCH_2CH_3), 62.05 (OCH_2CH_3) 103.63 ($CH(OCH_2CH_3)_2$), 112.09 (H_2C=Cq), 147.53 (H_2C=*Cq*), 218.41 (C=O), *m/z* (EI$^+$): 212.1 (5%, M^+) 167.1 (30 %, M^+-EtOH), (Found M^+, 212.1408. $C_{12}H_{20}O_3$ requires *M*, 212.1412).

Preparation of 1-(1-Diethoxymethyl-vinyl)-cyclopent-2-enol 3.25.

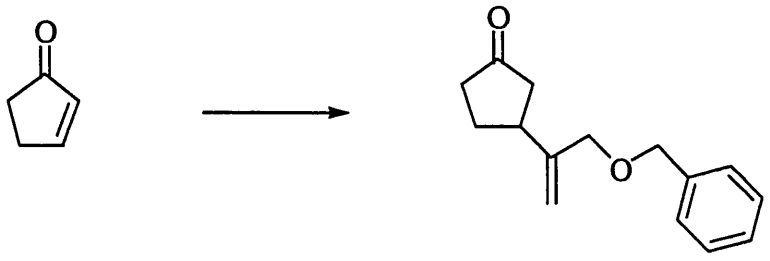


3.25

In a flame dried two-neck flask, a solution of **3.25** (0.198 g, 0.95 mmol) in Et_2O (1 mL) was cooled to –78 °C under an inert atmosphere of nitrogen. *t*-Butyl-lithium (0.56 mL of a 1.7 M solution in pentane, 0.95 mmol) was introduced dropwise with a glass syringe and the reaction was left stirring for 45 min at –78 °C. The lithiated alkene **3.19** was then transferred *via* a cannula to a slurry of CuI (8 mg, 0.047 mmol) in Et_2O (0.25 mL) at –78 °C and the resulting hetereogeneous solution was stirred for a further 30 min. Cyclopentenone (39 mg, 0.47 mmol) was introduced drop wise, the reaction mixture was left stirring at –78 °C for a further 2 hours and then quenched with a solution of saturated ammonium chloride (1 mL). The resulting solution was filtered, the organics separated and the aqueous extracted with Et_2O (2 × 1 mL). The

combined organics were then washed with water (2 mL), brine (2 mL) and dried over $MgSO_4$. The solvent was evaporated and the crude mixture chromatographed (SiO_2; light petroleum-ethyl acetate, 85:15) to yield *alcohol* **3.25** (0.075 g, 72 %) of a pale yellow oil, R_f (light petroleum-ethyl acetate, 75:25): 0.50, $\nu_{max}(CHCl_3)/cm^{-1}$: 3412 (O-H), 3041 (C-H), 2933 (C-H), 2829 (C-H), 1639 (C=C), 1131 (C-O-C), δ_H (400 MHz, $CDCl_3$): 1.25 (3H, t, *J* 7.2, OCH_2CH_{3A}), 1.26 (3H, t, *J* 7.2, OCH_2CH_{3B}), 2.03-2.10 (1H, m, $CH_AH_BC(OH)$), 2.16-2.23 (1H, m, $CH_BH_AC(OH)$), 2.27-2.34 (1H, m, $CH_CH_DCH{=}CH$), 2.50-2.55 (1H, m, $CH_DH_CCH{=}CH$), 3.48-3.55 (2H, m, $OCH_{2E}CH_3$), 3.57-3.74 (3H, m, $OCH_{2F}CH_3$), 5.05 (1H, bs, $CH(OCH_2CH_3)_2$), 5.18 (1H, d, *J* 1.2, $C{=}CH_GH_H$), 5.26-5.27 (1H, m, $C{=}CH_GH_H$), 5.78-5.81 (1H, m, $HC{=}CHCH_2$), 5.97-6.00 (1H, m, $HC{=}CHOH$), δ_C (100 MHz, $CDCl_3$): 15.50 (CH_3), 31.58 (CH_2), 39.72 (CH_2), 62.68 (CH_2), 62.73 (CH_2), 86.83 (Cq), 102.80 (CH), 112.62 (CH_2), 134.26 (CH), 135.69 (CH), 148.25 (Cq).

Preparation of 3-(1-Benzyloxymethyl-vinyl)-cyclopentanone 3.27.

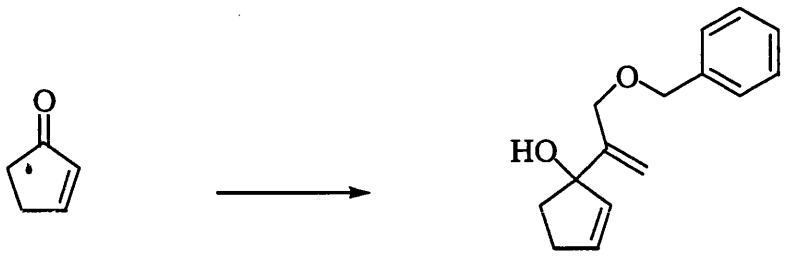


3.27

In a flame dried two-neck flask, a solution of **3.11** (0.44 g, 1.92mmol) in Et_2O (3 mL) was cooled to –78 °C under an inert atmosphere of nitrogen. *t*-Butyl-lithium (1.12 mL of a 1.7 M solution in pentane 1.90 mmol) was introduced dropwise with a glass syringe and the reaction was stirred for 45 min at –78 °C. The lithiated alkene

3.11 was then transferred *via* a cannula to a solution $[CuI.PBu_3]_4$ [2] (0.38 g, 0.24 mmol) in Et_2O (1 mL) at –78 °C. The resulting organocuprate (orange homogeneous solution) was stirred at this temperature for an additional 30 min. A solution of freshly distilled cyclopentenone (0.08 g, 0.96 mmol) in Et_2O (1 mL) was then added *via* another cannula to the organocuprate solution: a brown-grey precipitate formed immediately. After 1 hour at –78 °C the reaction mixture was quenched with a solution of saturated ammonium chloride (5 mL). The resulting solution was filtered, the organics separated and the aqueous extracted with Et_2O (3 × 5 mL). The combined organics were then washed with distilled water (7 mL), brine (7 mL) and dried over $MgSO_4$. The solvent was evaporated and the crude mixture chromatographed (SiO_2; light petroleum-ethyl acetate, 93:7) to yield (0.96 g, 45 %) of *ketone* **3.27** as a colourless oil. R_f (light petroleum-ethyl acetate, 75:25): 0.42, $\nu_{max}(CHCl_3)/cm^{-1}$: 2942 (C-H), 2856 (C-H), 1741 (C=O), 1649 (C=C), 1491 (C=C), 1453 (C=C), δ_H (400 MHz, $CDCl_3$): 1.77-1.86 (1H, m, $CH_AH_BCH_2CO$), 2.12-2.49 (5H, m, 5-membered ring protons), 2.90-2.95 (1H, m, $CHCH_2CO$), 4.00-4.08 (2H, m, OCH_2CCH_2), 4.51 (2H, s, $OCH_2C_6H_5$), 5.00 (1H, bs, $C=CH_DH_C$), 5.15 (1H, m, $C=CH_CH_D$), 7.27-7.38 (5H, m, aromatic protons), δ_C (100 MHz, $CDCl_3$): 28.65 (CH_2), 38.75 (CH_2), 40.04 (CH), 44.11 (CH_2), 72.51 (CH_2), 72.99 (CH_2), 111.94 ($C=CH_2$), 127.15 (CH), 127.88 (CH), 128.60 (CH), 138.23 (Cq), 147.17 (Cq), 218.28 (C=O), *m/z* (EI^+): 121 (10 %, $PhCH_2O=CH_2^+$), 91 (100 %, benzyl cation).

Preparation of 1-(1-Benzyloxymethyl-vinyl)-cyclopent-2-enol 3.24.

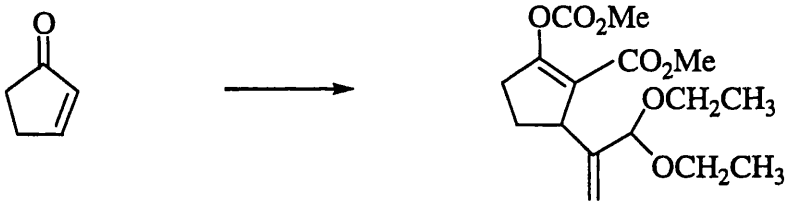


3.24

In a flame dried two-neck flask, a solution of **3.11** (0.32 g, 1.44 mmol) in Et_2O (2 mL) was cooled to –78 °C under an inert atmosphere of nitrogen. *t*-Butyl-lithium (0.85 mL of a 1.7 M solution in pentane 1.44 mmol) was introduced dropwise with a glass syringe and the reaction was left stirring for 45 min at –78 °C. The lithiated alkene **3.11** was then transferred *via* a cannula to a slurry of CuI (0.014 g, 0.072 mmol) in Et_2O (0.5 mL) at –78 °C and the resulting hetereogeneous solution was stirred for a further 30 min. Cyclopentenone (0.059 g, 0.72 mmol) was introduced drop wise, the reaction mixture was left stirring at –78 °C for a further 2 hours and then quenched with a solution of saturated ammonium chloride (2 mL). The resulting solution was filtrated, the organics separated and the aqueous extracted with Et_2O (2 × 1 mL). The combined organics were then washed with distilled water (2 mL), brine (2 mL) and dried over $MgSO_4$. The solvent was evaporated and the crude mixture chromatographed (SiO_2; light petroleum-ethyl acetate, 85:15) to yield *alcohol* **3.24** (0.094 g, 56 %) as a pale yellow oil, R_f (light petroleum-ethyl acetate, 75:25): 0.51, $\nu_{max}(CHCl_3)/cm^{-1}$: 3450 (O-H), 3063 (C-H), 3030 (C-H), 2926 (C-H), 2858 (C-H), 1636 (C=C), 1496 (C=C), 1455 (C=C), δ_H (400 MHz, $CDCl_3$): 1.99-2.06 (1H, m, CH_AH_BCOH), 2.14-2.20 (1H, m, CH_AH_BCOH), 2.27-2.36 (1H, m, $CH_CH_DCH{=}CH$), 2.28-2.50 (1H, m, $CH_DH_CCH{=}CH$), 4.13-4.23 (2H, m, $CH_2C{=}CH_2$), 4.55 (1H, d, *J*

12, OCH_EH$_F$C$_6$H$_5$), 4.57 (1H, d, *J* 12, OCH_FCH$_E$C$_6$H$_5$), 5.12-5.13 (1H, m, C=CH_GH$_H$), 5.15 (1H, bs, C=CH$_G$$H_H$), 5.75-5.78 (1H, m, *H*C=CHCH$_2$), 5.99-6.01 (1H, m, *H*C=CHCOH), 7.27-7.41 (5H, m, 5 × CH$_{Ar}$), δ_C (100 MHz, $CDCl_3$): 31.12 (CH_2), 38.90 (CH_2), 71.52 (CH_2), 72.37 (CH_2), 87.07 (Cq), 111.65 (*C*H$_2$=Cq), 127.46 (CH), 127.48 (CH), 128.16 (CH), 134.25 (CH), 135.03 (CH), 137.61 (Cq), 148.50 (Cq).

Preparation of 5-(1-Diethoxymethylvinyl)-2-methoxycarbonyloxycyclopent-1-enecarboxylic acid methyl ester 3.31.

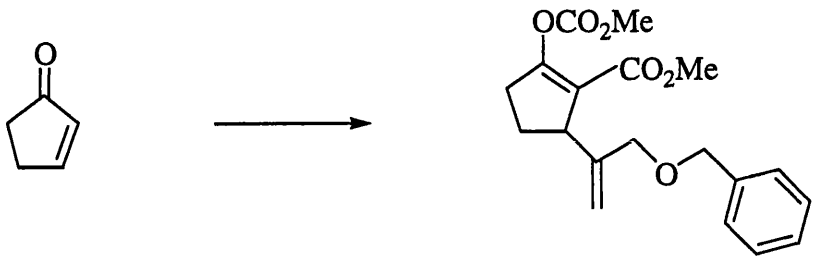


3.31

In a flame dried two-neck flask, a solution of **3.19** (7.14 g, 34.16 mmol) in Et_2O (50 mL) was cooled to –78 °C under an inert atmosphere of nitrogen. *t*-Butyl-lithium (20.10 mL of a 1.7 M solution in pentane 34.17 mmol) was introduced dropwise with a glass syringe and the reaction was stirred for 45 min at –78 °C. The lithiated alkene **3.19** was then transferred *via* a cannula to a solution $[CuI.PBu_3]_4$ [2] (6.7 g, 4.27 mmol) in Et_2O (20 mL) at -78° C. The resulting organocuprate (yellow homogeneous solution) was stirred at this temperature for an additional 30 min. A solution of freshly distilled cyclopentenone (1.40 g, 17.08 mmol) in Et_2O (5 mL) was then added *via* another cannula to the organocuprate solution: a yellow-grey precipitate formed immediately. After 1 hour at –78 °C, methylchloroformate (12.91 g, 136.64 mmol)

was added dropwise with a glass syringe. The reaction mixture was allowed to warm to room temperature and was left stirring overnight. A solution of saturated ammonium chloride (70 mL) was then introduced. The resulting solution was filtered, the organics separated and the aqueous extracted with Et_2O (3 × 30 mL). The combined organics were then washed with distilled water (2 × 40 mL), brine (2 × 40 mL) and dried over $MgSO_4$. The solvent was evaporated and the crude mixture was chromatographed (SiO_2; light petroleum-ethyl acetate, 92:8) to yield (3.30 g, 60 %) of *enol ester carbonate* **3.31** as a colourless oil. R_f (light petroleum-ethyl acetate, 90:10): 0.25, $\nu_{max}(CHCl_3)/cm^{-1}$: 2976 (C-H), 1769 (C=O), 1714 (C=O) 1654 (C=C), 1262 (C-O), 1202 (C-O), δ_H (400 MHz, $CDCl_3$): 1.22 (3H, t, *J* 6.6, OCH_2CH_{3A}), 1.23 (3H, t, *J* 6.6, OCH_2CH_{3B}), 1.81-1.87 (1H, m, $CH_CH_DCH_2CO$), 2.21-2.31 (1H, m, $CH_DH_CCH_2CO$), 2.47-2.54 (1H, m, CH_EH_FCO), 2.72-279 (1H, m, CH_EH_FCO), 3.43-3.53 (2H, m, $OCH_{2G}CH_3$), 3.57-3.66 (1H, m, $OCH_{2H}CH_3$), 3.67 (3H, s, OCO_2CH_3), 3.72-3.77 (1H, m, $HCC{=}CH_2$), 3.90 (3H, s, CO_2CH_3), 4.83 (1H, bs, $CH(OCO_2CH_3)_2$), 5.11 (1H, bs, $CHC{=}CH_GH_H$), 5.22 (1H, bs, $CHC{=}CH_HH_G$), δ_C (100 MHz, $CDCl_3$): 15.49 (OCH_2CH_{3A}), 15.54 (OCH_2CH_{3B}), 28.11 (CH_2), 31.94 (CH_2), 43.25 ($CHC{=}CH_2$), 51.54 (CO_2CH_3), 55.92 (OCO_2CH_3), 61.56 ($OCH_{2C}CH_3$), 62.32 ($OCH_{2D}CH_3$), 103.27 ($CH(OCH_2CH_3)_2$), 112.54 ($CHCq{=}CH_2$), 120.29 (Cq), 147.74 ($CHCq{=}CH_2$), 152.13 (Cq) 160.64 (CO_2CH_3), 163.57 (OCO_2CH_3), *m/z* (EI^+): 328.0 (5 %, M^+), 297.0 (15 %, M^+-OCH3), 282.0 (100 %, M^+-EtOH), ($C_{16}H_{24}O_7$ requires *M*: 328.1535. Found M^+: 328.1522).

Preparation of 5-(1-Benzyloxymethylvinyl)-2-methoxycarbonyloxycyclopent-1-enecarboxylic acid methyl ester 3.30.

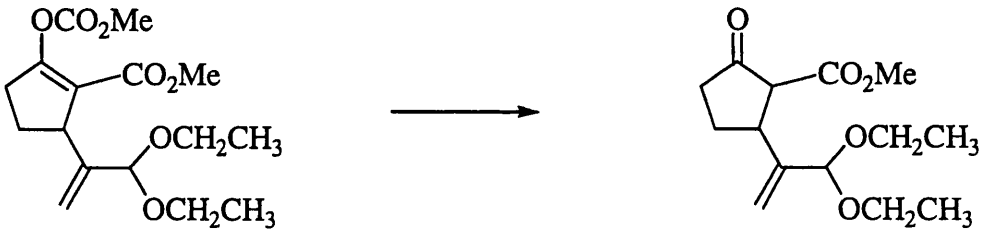


3.30

In a flame dried two-neck flask, a solution of **3.11** (0.44 g, 1.92 mmol) in Et_2O (3 mL) was cooled to –78 °C under an inert atmosphere of nitrogen. *t*-Butyl-lithium (1.13 mL of a 1.7 M solution in pentane, 1.92 mmol) was introduced dropwise with a glass syringe and the reaction was stirred for 45 min at –78 °C. The lithiated alkene **3.11** was then transferred *via* a cannula to a solution of $[CuI.PBu_3]_4$ [2] (0.38 g, 0.24 mmol) in Et_2O (1 mL) at -78° C. The resulting organocuprate (orange homogeneous solution) was stirred at this temperature for an additional 30 min. A solution of freshly distilled cyclopentenone (0.08 g, 0.96 mmol) in Et_2O (1 mL) was then added *via* another cannula to the organocuprate solution: a brown-grey precipitate formed immediately. After 1 hour at –78 °C, methylchloroformate (0.91 g, 9.6 mmol) was added drop wise with a glass syringe. The reaction mixture was allowed to warm up to room temperature and left stirring overnight. A solution of saturated ammonium chloride (5 mL) was then introduced. The resulting solution was filtered, the organics separated and the aqueous extracted with Et_2O (3 × 5 mL). The combined organics were then washed with distilled water (7 mL), brine (7 mL) and dried over $MgSO_4$. The solvent was evaporated and the crude mixture was chromatographed (SiO_2; light petroleum-ethyl acetate, 92:8) to yield *enol ester carbonate* **3.30** (0.079 g, 25 %) as a

colourless oil. R_f (light petroleum-ethyl acetate, 75:25): 0.39, $\nu_{max}(CHCl_3)/cm^{-1}$: 2942 (C-H), 2855 (C-H), 1766 (C=O), 1742 (C=O), 1659 (C=C), 1490 (C=C), 1436 (C=C), 1262 (C-O), 1201 (C-O), δ_H (400 MHz, $CDCl_3$): 1.75-1.82 (1H, m $CH_AH_BCH_2C(OCO_2CH_3)$), 2.21-2.37 (1H, m, $CH_BH_ACH_2C(OCO_2CH_3)$), 2.52-2.57 (1H, m, $CH_CH_DC(OCO_2CH_3)$), 2.73-2.83 (1H, m, $CH_CH_DC(OCO_2CH_3)$), 3.66 (3H, s, OCO_2CH_3), 3.70-3.73 (1H, m, $HCCCO_2CH_3$), 3.89 (3H, s, CO_2CH_3), 4.00-4.11 (2H, m, $H_2C=CCH_2O$), 4.45 (1H, d, *J* 11.6, $OCH_EH_FC_6H_5$), 4.56 (1H, d, *J* 11.6, $OCH_FH_EC_6H_5$), 5.06 (1H, bs, $C=CH_GH_H$), 5.10 (1H, app. d, *J* 1.7 $C=CH_GH_H$), 7.27-7.36 (5H, m, aromatic protons), δ_C (100 MHz, $CDCl_3$): 27.23 (CH_2), 31.81 (CH_2), 44.83 (CH), 51.38 (OCH_3), 55.65 (OCH_3), 71.86 (CH_2), 72.57 (CH_2), 111.81 (CH_2), 119.86 (Cq), 127.40 (CH), 127.57 (CH), 128.22 (CH), 138.28 (Cq), 147.34 (Cq), 151.79 (Cq), 160.05 (C=O), 163.28 (C=O),), *m/z* (EI^+): 346 (5 %, M^+), 238 (35 %, M^+-$PhCH_2OH$), 91 (100 %, benzyl cation), ($C_{19}H_{22}O_6$ requires *M* 346.1416 . Found M^+ 346.1430).

Preparation of 2-(1-Diethoxymethylvinyl)-5-oxo-cyclopentanecarboxylic acid methyl ester 3.37.

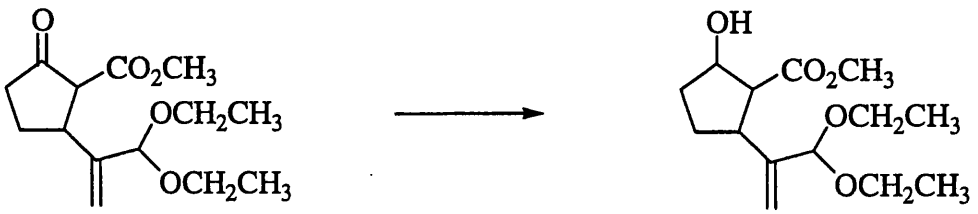


3.31 **3.37**

Enol ester carbonate **3.31** (0.07 g, 0.21 mmol) was stirred at room temperature for 2 hours with 2 mL of methanol and 0.5 mL of a 0.5 M (0.25 mmol) solution of sodium methoxide in methanol. Most of the methanol was then removed under vacuum.

Dichloromethane (2.5 mL) and 2.5 mL of saturated ammonium chloride were added to the residue. The organic layer was separated and the aqueous re-extracted with dichloromethane (3 × 2 mL). The combined organic layers were washed with brine (3 × 2 mL) and dried over $MgSO_4$. Evaporation of the solvent provided *keto ester* **3.37** as a clear oil (0.055 g, 95 %). R_f (light petroleum-ethyl acetate, 90:10): 0.24. $\nu_{max}(CDCl_3)/cm^{-1}$: 2976 (C-H), 2888 (C-H), 1758 (C=O), 1725 (C=O), 1114 (C-O-C), δ_H (400 MHz, $CDCl_3$): 1.21 (3H, t, *J* 7.1, OCH_2CH_{3A}), 1.22 (3H, t, *J* 7.1, OCH_2CH_{3B}), 1.78-1.84 (1H, m, $CH_CH_DCH_2CO$) 2.30-2.51 (4H, m, CH_2CO, $CH_CH_DCH_2CO$ and $CHC{=}CH_2$), 3.36-3.41 (4H, m, $CHCO_2CH_3$), 3.42-3.48 (2H, m, $OCH_{2E}CH_3$), 3.54-3.63 (2H, m, $OCH_{2F}CH_3$), 3.74 (3H, s, CO_2CH_3), 4.81 (1H, bs, $CH(OCH_2CH_3)_2$), 5.12 (1H, bs, $C{=}CH_GH_H$), 5.30 (1H, bs, $C{=}CH_HH_G$), δ_C (100 MHz, $CDCl_3$): 15.16 (CH_3), 27.86 (CH_2), 38.50 (CH_2), 42.66 (CH), 52.33 (CO_2CH_3), 60.22 (CH), 61.70 (CH_2), 62.20 (CH_2), 103.41 (CH), 113.58 (CH_2=Cq), 145.57 (CH_2=Cq), 169.12 (C=O), 210.72 (C=O), *m/z* (EI^+): 270.0 (>5 %, M^+), 224.0 (65 %, M^+-EtOH), 203.0 (100%, $EtOC{=}OEt^+$), ($C_{14}H_{22}O_5$ requires *M*: 270.1467. Found M^+: 270.1483).

Preparation of 2-(1-Diethoxymethylvinyl)-5-hydroxycyclopentanecarboxylic acid methyl ester 3.38.

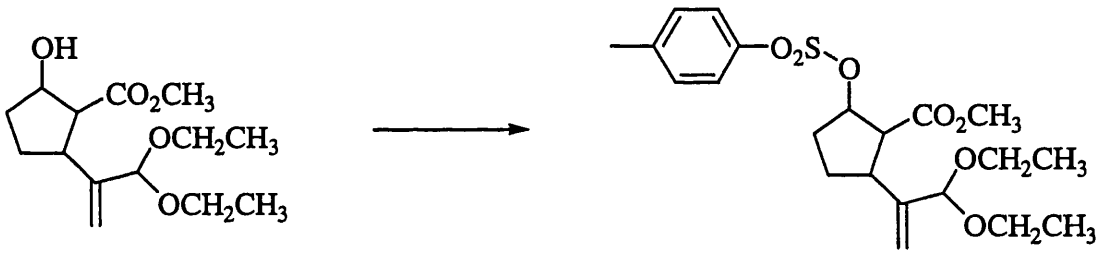


3.37 **3.38**

A solution of keto ester **3.37** (1.20 g, 4.44 mmol) in 35 mL of methanol was stirred at 0 °C under an inert atmosphere of nitrogen. Sodium borohydride (0.115 g, 3.03 mmol) was added portion wise and the mixture was stirred for an additional hour at 0 °C. The reaction was then quenched by the slow addition of 30 mL of brine, the mixture was extracted with Et_2O (3 × 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash-column chromatography (SiO_2, light petroleum-ethyl acetate, 80:20) to afford *hydroxy ester* **3.38** (1.00 g, 83 %) as a colourless oil and a mixture of inseparable sets of diastereoisomers (however, two sets of diastereoisomers are distinguished from each other in the ^{13}C NMR spectrum). R_f (light petroleum-ethyl acetate, 70:30), ν_{max}(neat)/cm^{-1}: 3458 (O-H), 2972 (C-H), 2872 (C-H), 1736 (C=O), 1641 (C=C), 1436 (C-H), 1200 (C-O), δ_H (400 MHz, $CDCl_3$): 1.21 (3H, t, *J* 7.1, OCH_2CH_{3A}), 1.22 (3H, t, *J* 7.1, OCH_2CH_{3B}), 1.50-1.59 (1H, m, $CH_CH_DCH2CHOH$), 1.72-1.83 (1H, m, $CH_CH_DCH_2CHOH$), 1.98-2.07 (1H, m, $CH2CH_EH_FCHOH$), 2.18-2.23 (1H, m, $CH_2CH_EH_FCHOH$), 2.78-2.93 (1H, m, $CHCO_2Me$), 3.17-3.40 (1H, m, $CH(C=CH_2)$), 3.41-3.49 (2H, m, $OCH_{2G}CH_3$), 3.53-3.62 (2H, m, $OCH_{2H}CH_3$), 3.70 (3H, s, CO_2CH_3), 4.38-4.51 (1H, m, CHOH) 4.77-4.79 (1H, m, $CH(OCH_2CH_3)_2$), 5.07-5.15 (1H, m, $C=CH_IH_J$), 5.25-5.26 (1H, m, $C=CH_IH_J$), δ_C (100 MHz, $CDCl_3$): major set of diastereoisomers: 15.53

(OCH_2CH_3), 30.75 (CH_2), 34.61 (CH_2), 42.57 (CH), 52.11 (OCH_3), 54.65 (CH), 61.72 ($OCH_{2B}CH_3$), 62.11 ($OCH_{2A}CH_3$), 74.53 (CHOH), 103.23 ($CH(OCH_2CH_3)$), 112.32 ($C=CH_2$), 147.72 ($CH_2=Cq$), 174.41 (C=O), minor set: 15.34 (OCH_2CH_3), 30.64 (CH_2), 34.22 (CH_2), 43.31 (CH), 52.17 (OCH_3), 58.26 (CH), 61.34 ($OCH_{2B}CH_3$), 62.17 ($OCH_{2A}CH_3$), 74.53 (CHOH), 103.34 (CH), 112.77 ($CH_2=Cq$), 147.38 ($CH_2=Cq$), 174.85 (C=O), *m/z* (FAB^+): 271.1 (47 %, M^+), 227.1 (100 %, M^+-EtOH), (M^+-EtOH requires *M* 227.1283. Found M^+-EtOH: 227.1260).

Preparation of 2-(1-Diethoxymethylvinyl-5-(toluene-4-sulfonyloxy)-cyclopentanecarboxylic acid methyl ester 3.39.

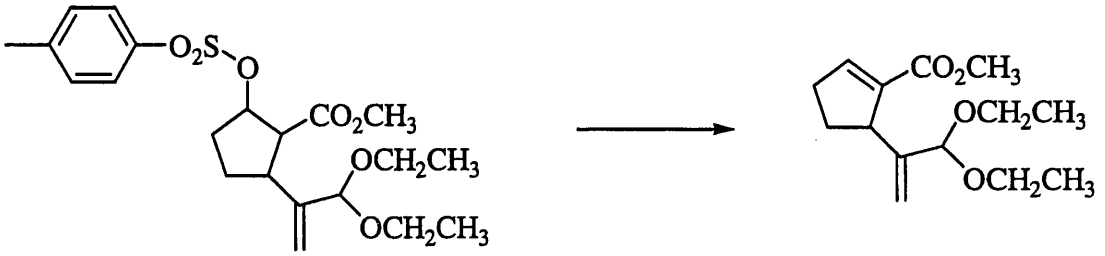


3.38 **3.39**

Hydroxy ester **3.38** (0.50 g, 1.84 mmol) was stirred in 16 mL of dry pyridine under an inert atmosphere of nitrogen. *p*-Toluenesulphonyl chloride (0.53 g, 2.79 mmol) was introduced and the reaction mixture was left stirring for three days at room temperature. The reaction was then quenched with saturated ammonium chloride (20 mL) and extracted with Et_2O (3 × 15 mL). The organics were combined, washed with water (2 × 20 mL), brine (2 × 20 mL) and dried over $MgSO_4$. The solvent was evaporated and the crude mixture chromatographed (SiO_2, light petroleum-ethyl acetate, 80:20) to afford the *tosylate ester* **3.39** (0.52 g, 66 %) as colourless oil and a mixture of inseparable diastereoisomers (two distinct sets however emerged in both

^{1}H and ^{13}C NMR interpretation). In the ^{1}H NMR spectrum, the AA'BB' system resulting from the aromatic protons resonance was approximated to an AB system R_f (light petroleum-ethyl acetate, 85:15): 0.25, ν_{max}(neat)/cm^{-1}: 2966 (C-H), 2924 (C-H), 1741 (C=O) 1589 (C=C), 1434, 1360 (S=O), 1188 (S=O), 1171 (C-OTs), δ_H (400 MHz, $CDCl_3$): major set: 1.15-1.20 (6H, m, $(OCH_2CH_3)_2$), 1.61-1.75 (2H, m, CH_2CH_2CHOTs), 1.92-2.20 (2H, m, CH_2CH_2CHOTs), 2.44 (3H, s, CH_3-Ar), 2.79-2.82 (1H, m, $CHCO_2CH_3$), 3.11-3.15 (1H, m, $HCC{=}CH_2$), 3.37-3.47 (2H, m, $CH(OCH_{2A}CH_3)_2$), 3.49 (3H, s, OCH_3), 3.53-3.70 (2H, m, $CH(OCH_{2B}CH_3)_2$), 4.76 (1H, bs, $CH(OCH_2CH_3)_2$), 4.99-5.32 (3H, m, CH_2=C and CH-OTs), 7.26-7.35 (2H, m, CH_{Ar}), 7.74-7.90 (2H, m, CH_{Ar}), minor set: 1.15-1.20 (6H, m, $(OCH_2CH_3)_2$), 1.61-1.75 (2H, m, CH_2CH_2CHOTs), 1.92-2.20 (2H, m, CH_2CH_2CHOTs), 2.45 (3H, s, CH_3-Ar), 2.79-2.82 (1H, m, $CHCO_2CH_3$), 3.11-3.15 (1H, m, $HCC{=}CH_2$), 3.37-3.47 (2H, m, $O(CHCH_{2A}CH_3)_2$), 3.54 (3H, s, OCH_3), 3.54-3.70 (2H, m, $OCH(CH_{2B}CH_3)_2$), 4.70 (1H, bs, $CH(OCH_2CH_3)_2$), 4.99-5.32 (3H, m, CH_2=C and CH-OTs), 7.26-7.35 (2H, m, CH_{Ar}), 7.74-7.90 (2H, m, CH_{Ar}), δ_C (100 MHz, $CDCl_3$): major set: 15.47 (OCH_2CH_3), 22.07 (CH_3-Ar), 29.94 (CH_2), 32.87 (CH_2), 41.51 (CH), 52.26 (OCH_3), 56.08 ($CHCO_2CH_3$), 62.26 ($OCH_{2B}CH_3$), 61.90 ($OCH_{2A}CH_3$), 83.63 (CHOTs), 103.82 ($CH(OCH_2CH_3)_2$), 112.99 (CH_2=Cq), 127.96 (CH_{Ar}), 129.88 (CH_{Ar}), 134.35 (Cq_{Ar}), 144.73 (Cq_{Ar}), 146.71 (Cq=CH2), 170.19 (C=O), minor set 15.50 (OCH_2CH_3), 22.07 (CH_3-Ar), 29.94 (CH_2), 32.96 (CH_2), 44.44 (CH), 52.26 (OCH_3), 54.08 ($CHCO_2CH_3$), 61.90 ($OCH_{2B}CH_3$), 62.26 ($OCH_{2A}CH_3$), 85.50 (CHOTs), 103.82 ($CH(OCH_2CH_3)_2$), 113.50 (C=CH2), 128.17 (CH_{Ar}), 129.97 (CH_{Ar}), 134.35 (Cq_{Ar}), 144.73 (Cq_{Ar}), 146.26 ($Cq=CH_2$), 173.31 (C=O), *m/z* (EI^+): 426.1 (25 %, M^+), 381.1 (15 %, M^+-EtOH), 103.1 (100 %, $EtOC{=}OEt^+$), (Found M^+ 426.1700. $C_{21}H_{30}O_7S$ requires *M* 426.1712).

Preparation of 5-(1-Diethoxymethyl-vinyl)-cyclopent-1-enecarboxylic acid methyl ester 3.40.

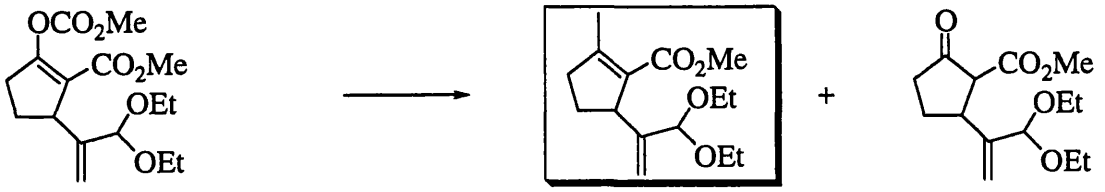


3.39 **3.40**

Tosylate ester **3.39** (0.160 g, 0.37 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.085 g, 0.56 mmol) were stirred in dry DMF (5 mL). The resulting solution was heated to 80 °C for 1 hour. The reaction was then cooled to room temperature and quenched with 10 mL of water and 10 mL of Et_2O. The organic layer was separated from the aqueous layer, which was re-extracted with Et_2O (3 × 5 mL). The combined organics were washed with a solution of saturated ammonium chloride (10 mL), distilled water (10 mL), brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated to afford *unsaturated ester* **3.40** (0.062 g, 66 %) as a pale yellow oil. R_f (light petroleum-ethyl acetate, 85:15): 0.48, $\nu_{max}(CHCl_3)/cm^{-1}$: 2960 (C-H), 2895 (C-H), 1723 (C=O), 1630 (C=C), 1436 (s), 1283 (C-O), δ_H (400 MHz, $CDCl_3$): 1.23 (3H, t, *J* 7.4, OCH_2CH_{3A}), 1.24 (3H, t, *J* 7.4, OCH_2CH_{3B}), 1.83-1.90 (1H, m, $CH_CH_DCH_2CHCCO_2Me$), 2.22-2.32 (1H, m, $CH_DH_CCH_2CHCCO_2Me$), 2.38-2.54 (2H, m, CH_2HCCCO_2Me), 3.43-3.68 (5H, m, 2 × OCH_2CH_3 and $HCC=CH_2$), 3.69 (3H, s, CO_2CH_3), 4.86 (1H, s, $HC(OCH_2CH_3)_2$), 4.86 (1H, s, $CHC=CH_EH_F$), 5.19-5.20 (1H, m, $HCC=CH_EH_F$) 6.94 (1H, td, *J* 3.0 and 1.6, $HC=CCO_2Me$), δ_C (100 MHz, $CDCl_3$): 15.52 (OCH_2CH_{3C}); 15.48 (OCH_2CH_{3D}), 32.06 (CH_2), 32.30 (CH_2) 45.38 ($HCC=CH_2$), 51.62 (OCH_3), 61.27 ($OCH_{2B}CH_3$), 62.11 ($OCH_{2A}CH_3$), 103.12

(*C*H(OCH$_2$CH$_3$)$_2$), 111.93 (C=*C*H$_2$), 138.59 (Cq), 145.95 (*C*H=CCO$_2$Me), 148.34 (Cq), 165.68 (CO), *m/z* (FAB$^+$): 253.1 (45 %, M$^+$-H), 209.1 (100%, [M$^+$-H]-EtOH), (Found M$^+$ 254.1506. $C_{14}H_{22}O_4$ requires *M* 254.1518).

Preparation of 5-(1-Diethoxymethyl-vinyl)-2-methyl-cyclopent-1-enecarboxylic acid 3.44.



3.31 **3.44** **3.37**

A flame dried two-neck flask containing a suspension of copper(I) cyanide (0.011 g, 0.12 mmol) in dry THF (1 mL) was cooled down to –78 °C under an inert atmosphere of nitrogen. Methyl lithium (0.15 mL of a 1.6 M solution in Et_2O, 0.24 mmol) was then added dropwise with a glass syringe. On completion, the reaction mixture was warmed to –40 °C for 10 minutes; the resulting clear homogeneous solution was then cooled to –78 °C. A solution of unsaturated ester **3.31** (0.015 g, 0.059 mmol) in THF (0.5 mL) was added dropwise *via* a cannula and the resulting solution was stirred for an hour at –78 °C. The reaction mixture was quenched with a solution of saturated ammonium chloride (2 mL). The resulting solution was filtered, the organics separated and the aqueous extracted with Et_2O (2 × 1 mL). The combined organics were then washed with distilled water (2 mL), brine (2 mL) and dried over $MgSO_4$. The solvent was evaporated and the crude mixture chromatographed (SiO_2; light petroleum-ethyl acetate, 90:10) to yield (28 mg, 58 %) of keto ester **3.37** and (16 mg, 33 %) of *unsaturated ester* **3.44** as a pale yellow oil;

R_f (light petroleum-ethyl acetate, 80:20): 0.25, δ_H (400 MHz, $CDCl_3$): 1.23 (3H, t *J* 7.2, OCH_2CH_{3A}), 1.25 (3H, t *J* 7.2, OCH_2CH_{3B}), 1.84-2.00 $CH_2CH_2C(CH_3)=C(CO_2Me)$), 2.14-2.23 (1H, m, $CH_AH_BC(CH_3)=C(CO_2Me)$), 2.35-2.44 (1H, m, $CH_AH_BC(CH_3)=C(CO_2Me)$), 2.50 (3H, d *J* 1.2, $CH_3C=C(CO_2Me)$), 3.41-3.54 (2H, m, $OCH_{2C}CH_3$), 3.58-3.69 (2H, m, $OCH_{2D}CH_3$), 3.70 (3H, s, CO_2CH_3), 3.81 (1H, d *J* 8, $CH_2CHC=CH_2$), 4.86 (1H, s, $CH(OCH_2CH_3)$ or $H_EH_F=CC(OCH_2CH_3)_2$), 4.91 (1H, s, $CH(OCH_2CH_3)$ or $H_EH_F=CC(OCH_2CH_3)_2$), 5.17 (1H, d *J* 1.2, $H_EH_F=CC(OCH_2CH_3)_2$), δ_C (100 MHz, $CDCl_3$): 13.16 ($CH_3C=C(CO_2Me)$), 15.56 (OCH_2CH_{3D}), 15.59 (OCH_2CH_{3C}), 26.01 (CH_2) 38.60 (CH_2), 40.81 ($CHC=CH_2$), 54.45 (CO_2CH_3), 60.29 ($OCH_{2B}CH_3$), 62.38 ($OCH_{2A}CH_3$), 102.57 ($CH(OCH_2CH_3)_2$), 111.70 ($C=CH_2$), 116.49 (Cq), 147.87 (Cq), 165.28 (CO), *m/z* (FAB^+): 269.1 (30 %, M^++H), 223.1 (100 %, $[M^+$+H]-EtOH).

4.4 References

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